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ORIGINAL RESEARCH

Therapeutic Journey and Economic Burden of Patients with Myasthenia Gravis in Italy: Results of a Real-World Analysis

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ABSTRACT

AIM: This analysis investigated the population with Myasthenia Gravis (MG) in Italy, to describe epidemiology, mortality, patients' characteristics, comorbidity profile, therapeutic management, and healthcare consumption and related costs.
METHODS: From 2012 to 2021, MG patients were identified in administrative flows of healthcare entities through hospitalization discharge diagnosis or exemption code for MG or a pyridostigmine prescription. Medications and comorbidities were searched before inclusion and healthcare costs were analysed at 1-year follow-up. Epidemiology estimates were reported as cases/100,000 people, and mortality rates, stratified by age classes and gender, were assessed during 2019. MG patients were compared with age- and gender-matched subjects without MG.
RESULTS: At the end of 2021, MG prevalence was 35.1/100,000 and incidence 4.7/100,000 people. Mortality in 2019 was 3.2% in overall MG sample, and tended to rise in males and elderly patients. About 90% received MG-related treatments, namely pyridostigmine, corticosteroids and immunosuppressants (81.3%, 76.9% and 26.1% of patients respectively). Unsurprisingly, the yearly healthcare resource consumption/patient was higher in MG patients than in non-MG subjects ($p<0.001$), resulting in increased annual direct costs for MG patients (€5,495 vs €823, $p<0.001$), related to expenses for hospitalizations (mostly related to nervous system and respiratory system), drugs and outpatient services.
CONCLUSIONS: In this study, incidence and prevalence of MG estimated in Italy were similar to other European countries and mortality rates were from 2 to 3-times higher than general population. Despite the current treatment options and adherence to guidelines for MG management, the clinical and economic burden of the disease remains high.

Keywords

Myasthenia Gravis; Therapeutic management; Cost analysis; Real-world evidence; Incidence; Prevalence; Mortality

INTRODUCTION

Myasthenia Gravis (MG) is a rare disease that affects the postsynaptic membrane at the neuromuscular junction, characterized by weakness and fatigability of skeletal muscle with heterogeneous clinical presentation [1-3]. Although the exact etiology is not yet fully understood, MG is an autoimmune disorder related to circulating autoantibodies mainly against the acetylcholine receptor (AChR) [4], the muscle-specific receptor tyrosine kinase (MuSK), and LRP4 [5].

MG can present at any age. The juvenile form is defined as MG occurring before 18 years of age [6]. In adults, MG has a different time of onset between genders: women show a bimodal distribution, with peaks around 30 and 50 years of age, while in men MG rates increase with older age, with peaks between 60 and 89 years [6,7].

The incidence and prevalence of MG are highly variable worldwide along with ethnicity, gender, and environmental factors [8-12]. The latest global data updated to 2019 reported an incidence rate of AChR antibody-positive MG ranging between 4 and 18 per million person-year, and a prevalence of MG between 1.5 and 36.71 cases/100,000 people, depending on the geographic location, which corresponds to an estimate of 56,000-123,000 patients in Europe and 60,000 in the United States [9]. In Italy, the prevalence of MG in 2018 has been recently estimated at 29.3 cases per 100,000 people [13].

Patients have fluctuating weakness and fatigability that commonly worsen with physical activity, and improve with rest. The involved muscles belong to the ocular, generalized, bulbar and respiratory groups in variable combinations [14-16]. The most typical initial symptom is extraocular muscle weakness with double vision and/or eyelid ptosis that occurs in about 85% of patients and often progresses to generalized MG involving the bulbar, axial, and limb muscles within two years. Bulbar muscle weakness can be the initial presentation in 15% of patients; in these cases, the involvement of facial muscles causes an expressionless face or snarl smile; in rare instances the severe neck muscle involvement can lead to the dropped-head syndrome. Limb weakness generally involves the proximal muscles to a larger extent than distal muscles, and upper limbs are more affected than lower limbs. Myasthenic crisis is due to the involvement of intercostal muscles and diaphragm, thus representing an important medical emergency [1]. The Myasthenia Gravis Foundation of America (MGFA) has developed a clinical classification for the disease into different classes based on clinical features [17].

Therapy schedules indicated for MG depend on disease severity (i.e. ocular vs. generalized), and the type of presentation, especially in case of bulbar dysfunction, exacerbation or crisis. The complete stable remission (CSR) has been recorded in a minority of patients. The ultimate goal of treatment should be the achievement of the condition of pharmacological remission (no symptoms or signs of MG, PR), or a condition of "Minimal Manifestation Status" (MM), as defined by the MGFA when "the patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination" [17].

To have a measurement of MG symptoms, functional status and response to treatments, the Myasthenia Gravis Activities of Living (MG-ADL) has been introduced, consisting of an 8-item patient-reported scale [18]. Recently, the concept of "Minimal Symptom Expression" (MSE), which is based on the MG-ADL and a 15-item MG quality of life questionnaire, is being adopted. The achievement of MSE has been defined by a MG-ADL total score of 0-1 or MG-QOL15 total score of 0-3 [19,20]. Consistent with the international guidelines [21], the Italian recommendations indicate the anticholinesterase inhibitor pyridostigmine as frontline symptomatic treatment of MG [22]. Most of MG patients respond to pyridostigmine that is commonly well-tolerated. Steroids are used as rapid-acting therapy when severely disabling symptoms are not controlled with pyridostigmine. On the other hand, due to the known side effects of steroids, longer-term treatments are based on steroid-sparing immunosuppressive regimens, with azathioprine as first option, and then mycophenolate, cyclosporine, tacrolimus, and cyclophosphamide [20].

Long-term immunosuppression with rituximab has been proposed for patients with MuSK associated MG [21,22]. However, disease management remains challenging in around 10% of MG patients who do not respond adequately to current therapies [22,23]. These patients are deemed as treatment refractory, or treatment intolerant: among them, up to 80% fail to achieve complete and stable remission. Even though MG patients with autoantibodies against MuSK appear to more susceptible to become treatment refractory compared to anti-AChR positive ones, both serotypes are anyhow represented among the refractory population [23].

Therapeutic plasma exchange (TPE) and intravenous immunoglobulins (IVIg) are indicated as short-term treatments in MG patients with life-threatening signs (i.e. respiratory insufficiency or dysphagia), before surgery for bulbar dysfunction, when other treatments are ineffective, or when achieving rapid removal of pathogenic antibodies is needed [20,21]. TPE and IVIg can be also used before starting corticosteroid therapy to prevent or minimize exacerbations [21,22].

The latest gidelines of the American Academy of Neurology updated to 2020, recommend treatment with thymectomy plus prednisone for patients with nonthymomatous generalized MG with anti-AChR antibodies, which appears to be more effective than prednisone alone for increasing the likelihood of achieving MM status (with 20% risk difference at 36 months) [24].

The lack of a national pathology register, together with the relatively small although rising numbers of MG patients, makes it difficult to collect epidemiological, clinical and therapeutic information on disease burden in Italy. These flaws also result in an uncertain estimation of the actual economic burden of this pathology for Italian National Health Service (INHS), which up to now is unable to track the direct costs deriving from the management of MG patients that might be feasibly underestimated.

In this context, the purpose of the present analysis was to investigate the epidemiology of MG, in terms of prevalence, incidence and mortality rates, the demographic characteristics, comorbidity profile and therapeutic management of MG population, with the resulting healthcare resource use (HCRU) and direct costs for INHS in a setting of real clinical practice in Italy.

METHODS

Data source

A retrospective observational analysis was conducted on data collected from the administrative flows of a pool of Italian healthcare bodies of the regions Piedmont, Veneto, Liguria, Umbria, Abruzzo, Lazio, Molise, Campania and Apulia, corresponding to a catchment area of 9.2 million health-assisted residents. These entities were selected for completeness of information within the study period. The administrative databases contain all data on healthcare resources covered by the INHS, thus they allow to track the reimbursed drug prescriptions, hospital stays, and service provisions. Specifically, the administrative databases used for this analysis were beneficiaries, pharmaceuticals, hospitalizations, outpatient specialist services (OSS) and exemption databases, as previously described [25]. In particular, drug prescriptions were identified through the Anatomical Therapeutic Chemical (ATC) classification system and hospital discharge diagnoses through the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, Diagnosis Related Group (DRG) and DRG related charge (provided by Health System).

To ensure privacy, data were irreversibly anonymized assigning a univocal numerical code to each participating subject, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). All the results are provided as aggregated summaries that do not allow identifying individual patients, either directly or indirectly. Informed consent was waived since obtaining it was impossible for organizational reasons (pronouncement of the Data Privacy Guarantor Authority, General Authorization for personal data treatment for scientific research purposes—n.9/2014). The protocol was notified and approved by the local Ethics Committee of the healthcare bodies involved.

Patients

The population in analysis was included between 2011 and 2021, depending on data availability of each participating unit (in some cases, the inclusion period started later than January 2011 or ended before December 2021). The patients were identified by the presence of: (i) 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); OR (ii) at least one active exemption code for MG (RFG101; 034); OR (iii) at least one prescription of pyridostigmine (ATC code N07AA02) AND one AChR antibody test (procedure code 90.53.9), in the absence of the criteria (i) and (ii). The index-date was that of the first detection of one of the inclusion criteria. The characterization period used for patients' baseline assessment before inclusion was one year for the search of drug prescriptions,

and all period of available data for hospitalizations. The patients were followed-up for at least one year from the index-date to end of data availability or death, whichever occurred first.

The exclusion criteria were the following: (i) patients with less than 1 year of data availability after index-date; (ii) patients without continuous data availability during the study period (e.g. those who moved to another region); (iii) patients included by pyridostigmine prescription (without exemption/hospitalization for MG) with diagnoses 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 for spinal cord injury (one hospitalization with diagnosis at any levels for spinal cord injury [ICD-9-CM codes: 806, 952]).

A group of subjects without MG (non-MG cohort) matched exactly for age and sex distribution was selected for comparative analyses of the most frequent drugs and hospitalizations in the year preceding index-date, and of the average costs per person at the first year of follow-up.

Epidemiological data: incidence, prevalence and mortality rate of MG

The trends over time of MG incidence, prevalence and mortality were evaluated from 2012 to 2021, collecting data from some healthcare units with available data for those years.

A thorough and up-to date analysis of age- and gender-specific prevalence and incidence was provided for year 2021 (10-year-age/gender groups). The assignment to an age group was based on the age of patient at index-date.

The incidence of MG was calculated as the number of MG patients identified in 2021 without any past record related to myasthenia in all previously available period (at least 1 year) per 100,000 health-assisted subjects in 2021 who were alive on 1 January 2021.

The prevalence of MG was calculated as the number of prevalent MG patients alive on 31 December 2021 per 100,000 health-assisted subjects who were alive on 31 December 2021. Prevalence was reported as cases per 100,000 people in 10-year-age/gender groups.

The one-year crude mortality rate of patients was calculated for year 2019, to avoid possible interference due to COVID-19 pandemic [26]. Mortality rates were reported for all MG patients and after stratification by age groups and gender. Data were then compared with the mortality rate of the general population in Italy during the same year [27].

Baseline variables

The demographic characteristics of the included population were collected at index-date. Age was reported in years and by 10-year-age classes, sex distribution was presented as percentage of male subjects. The general clinical status of MG patients was evaluated using the Charlson Comorbidity Index (CCI), a tool to predict 10-year survival summing the weight of 19 comorbid conditions [28]. Patients' past history was then further analyzed by searching for the presence of the following conditions frequently associated with MG [29,30] or with extensive use of corticosteroids: diabetes, arrhythmias, dyslipidemia, osteoporosis, hypertension, depression, use of anti-infective agents, myopathies, osteonecrosis of the femoral head, glaucoma and cataract. The diseases were searched using hospitalization and exemption codes exploring all available data before the index-date, and treatment codes in the year before the index-date, as proxy of diagnosis.

Moreover, the following treatments for MG were evaluated during all available period preceding the index-date and during follow-up: pyridostigmine (ATC code N07AA02), systemic corticosteroids (ATC code H02), azathioprine (ATC code L04AX01), cyclophosphamide (ATC code L01AA01), cyclosporine (ATC code L04AD01), tacrolimus (ATC code L04AD02)], eculizumab (ATC code L04AA25), TPE or plasmapheresis (ICD-9-CM 99.71, 99.76), IVIg (ICD-9-CM 99.14), thymectomy (procedure code ICD-9-CM 07.8).

Treatment patterns were evaluated among adult patients during follow-up in terms of: (i) numbers of treatment, i.e. the changes in number for adult patients with at least 1 treatment; (ii) switch, defined as a change to a therapeutic class different from the previous one; (iii) add-on, defined as an addition of another therapeutic to the previous one.

HCRU and direct costs for the INHS

The HCRU was calculated as number of resources provided per adult patient during the year before inclusion and after the first year of follow-up in terms of drug treatments, hospitalizations (ordinary and day hospital) and OSS, namely laboratory tests, specialistic visits, and diagnostic procedures.

The deriving direct costs were then computed for alive patients after excluding outliers (those values were more than 3 times the standard deviation over the mean value). Healthcare direct costs for the non-MG population were also calculated. Cost analysis was carried out from the perspective of the INHS. Costs of medications were determined using the INHS purchase price. Causes of hospitalizations were identified by Major Diagnostic Category (MDC), and hospitalization costs were assessed by means of DRG tariffs, which represent the reimbursement reference of the INHS for healthcare providers.

Statistical analysis

A descriptive statistical analysis was carried out for continuous variables presented as mean with standard deviation and categorical variables presented as frequency counts and percentages. Comparisons were made by Student's t test or by nonparametric test Mann-Whitney U test, as appropriate. Chi-square test, or Fisher's exact test when expected frequencies are less than 5, were used to compare categorical variables. In subgroups consisting of less than four patients, data were not issuable (N.I.) for data privacy, since the results might be potentially referrable to single individuals, in compliance with the *Codice in materia di protezione dei dati personali* [Code for protection of personal data] (D. Lgs. 196/2003). A p value <0.05 was considered as statistically significant and the analyses were performed by STATA SE, version 12.0.

RESULTS

Epidemiology estimates

The prevalence and incidence of MG per 100,000 people in overall and adult population during the period 2012-2021 are shown in Figure 1A and 1B, respectively.

The differences in epidemiological estimates in MG patients stratified by 10-year age classes and gender are shown in Figure 2.

At the end of the observation period (31 December 2021), the prevalence of MG in our sample of the Italian population was 35.1/100,000 people, 33.1 in men and 37.1 in women, with a rising trend over the last 10 years, more pronounced among younger women, compared to male predominance in patients aged over 60 years. Considering the adult population alone, the prevalence rose up to 41.4/100,000 individuals. The incidence estimates revealed 4.7 new MG cases per 100,000 individuals in the adult population for year 2021. The trends in yearly incidence rates over time in the period 2012-2021 showed a zenith in 2018, followed by a marked decrease after 2020, that might be due to underdiagnosed cases during the COVID-19 pandemic outbreak.

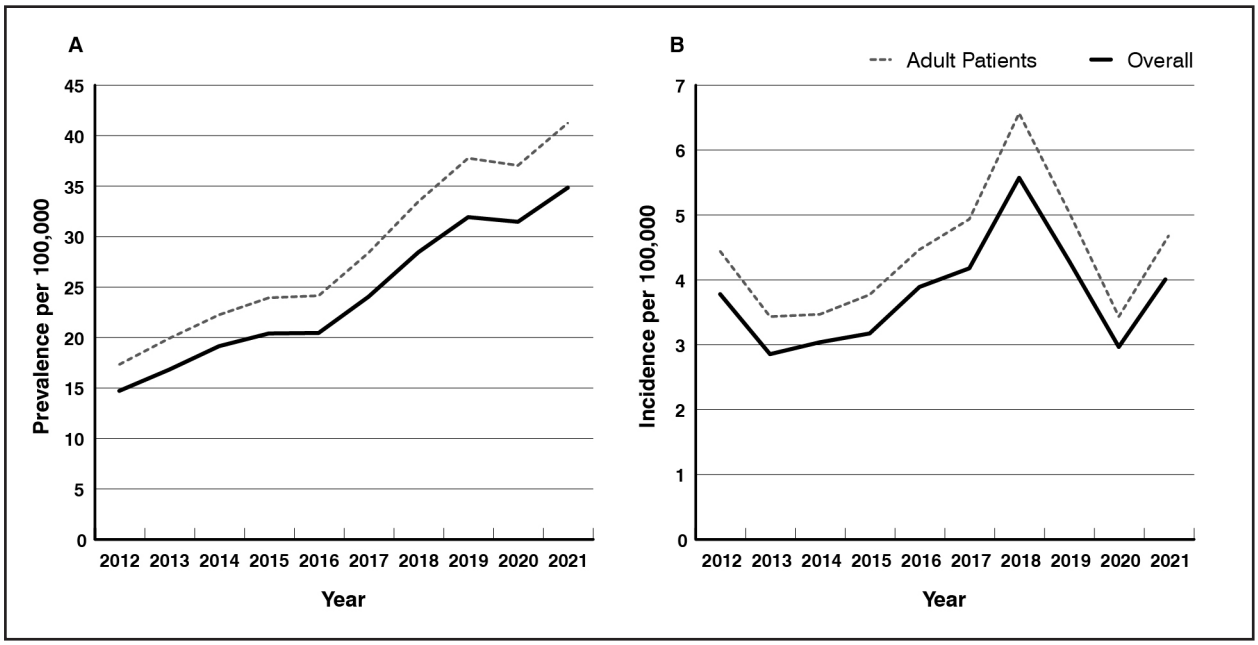


Figure 1. *Prevalence (A) and annual incidence (B) of MG per 100,000 people in overall and adult population in the period 2012-2021*

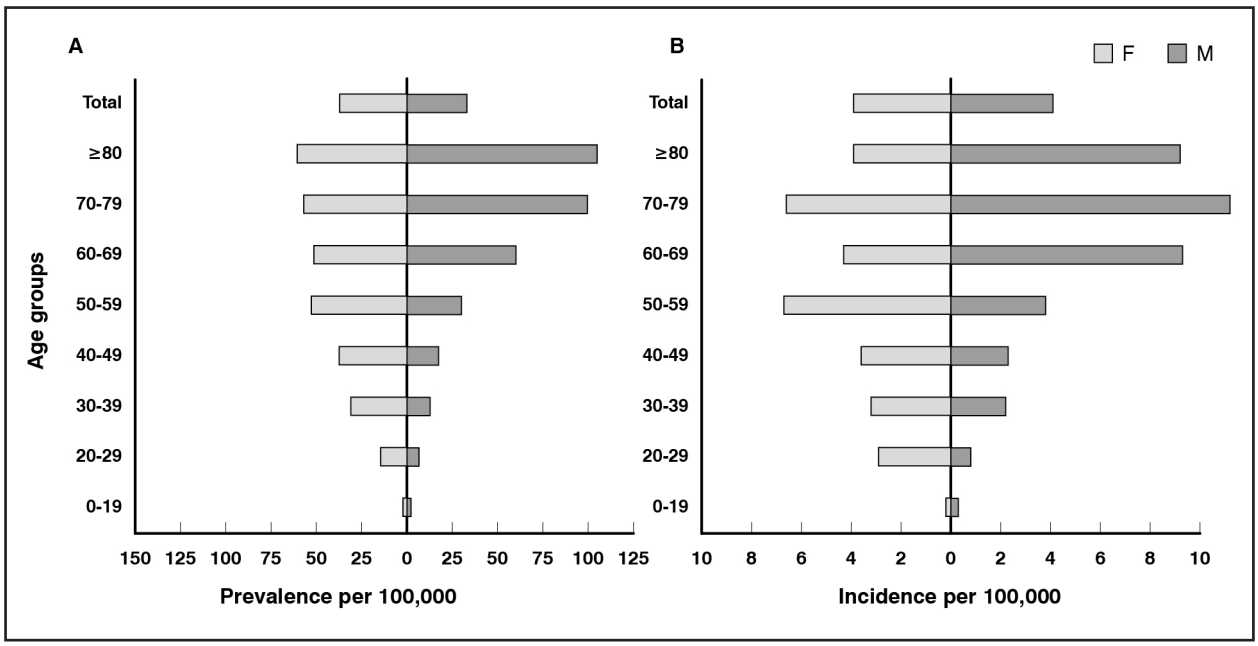
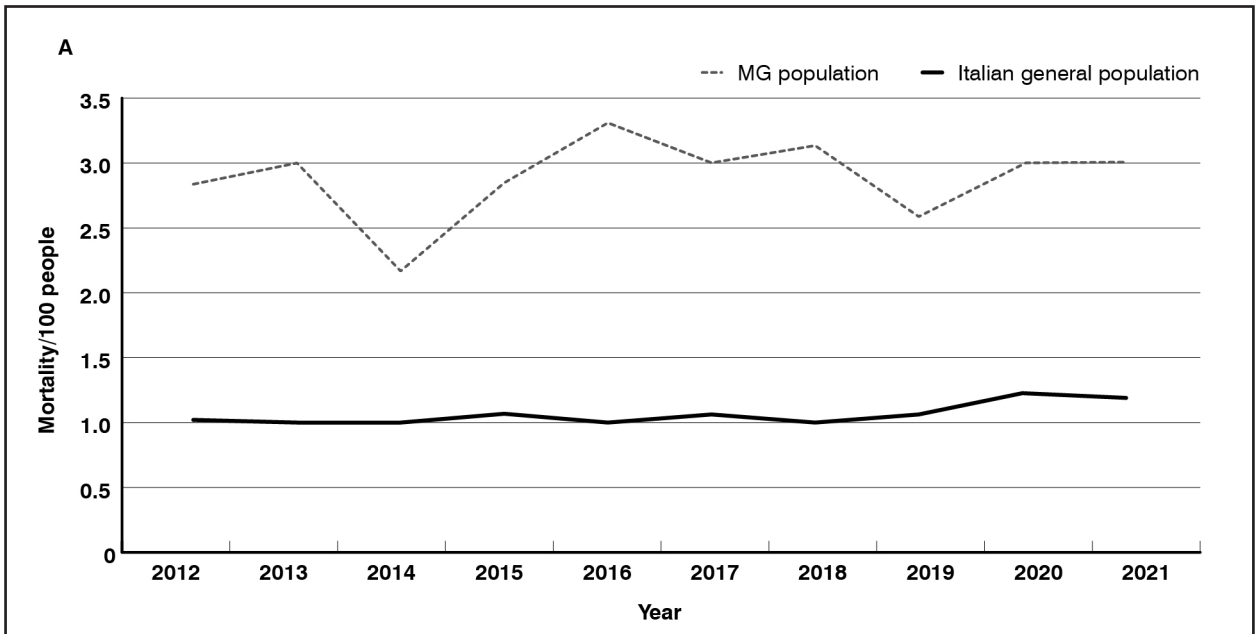


Figure 2. *Prevalence (A) and annual incidence (B) of MG per 100,000 people by gender and 10-year age classes in 2021*



B

Mortality rates of the MG sample in 2019			
Age Classes	**M**	**F**	**Total**
0-19	0.0	0.0	0.0
20-49	0.0	0.2	0.2
50-59	0.6	1.1	0.9
60-69	2.3	0.8	1.6
70-79	3.2	2.8	3.1
≥80	8.0	7.2	7.6
Total	**3.2**	**2.1**	**2.6**

C

Mortality rates of the Italian population in 2019			
Age Classes	**M**	**F**	**Total**
0-19	0.0	0.0	0.0
20-49	0.1	0.1	0.1
50-59	0.4	0.2	0.3
60-69	1.0	0.5	0.8
70-79	2.7	1.6	2.1
≥80	10.5	9.0	9.6
Total	**1.0**	**1.1**	**1.1**

Figure 3. *(A) Mortality rates per 100 people in MG sample analyzed and in the Italian general population over the period 2012-2021; (B) mortality rates per 100 people in MG sample analyzed with gender stratification in 2019; (C) mortality rates per 100 people in the Italian population with gender stratification in 2019 [27]*

As illustrated in Figure 3A, the mortality rates showed some fluctuations over the years, but were always markedly higher that those reported for the general population by the Italian Institute of Statistics (ISTAT) [27]. The mortality rates stratified by gender and age classes were analyzed for year 2019 (chosen here to avoid the bias in death counts due to COVID-19 pandemic), on patients alive on 31 December 2018, in the sample population of this analysis (Figure 3B) and in the Italian population (Figure 3C). In both cases, the mortality rates were similar between genders in younger MG subjects (0-49 years), but tended to be higher in male than in female patients aged 60 years.

Characteristics of the population

Overall, 2,412 patients with MG were included in the analysis, 1,118 males (49.3%) and 1,224 (50.7%) females, with a mean age of 61.1 years. Women were younger that men (M vs

Characteristics	Patients with MG	Male	Female	p
Patients (n)	2,412	1,188	1,224	
Age at inclusion (years)	61.1 ± 17.5	64.4 ± 15.8	58.0 ± 18.5	**<0.001**
CCI	0.7 ± 1.2	0.8± 1.3	0.6 ± 1.1	**<0.001**
Hypertension, n (%)	1,263 (52.4)	701 (59)	562 (45.9)	**<0.001**
Dyslipidemia, n (%)	563 (23.3)	314 (26.4)	249 (20.3)	**<0.001**
Diabetes, n (%)	349 (14.5)	212 (17.8)	137 (11.2)	**<0.001**
Depression, n (%)	340 (14.1)	107 (9)	233 (19)	**<0.001**
Osteoporosis, n (%)	160 (6.6)	40 (3.4)	120 (9.8)	**<0.001**
Arrhythmias, n (%)	73 (3.0)	38 (3.2)	35 (2.9)	0.627
Cataract, n (%)	36 (1.5)	17 (1.4)	19 (1.6)	0.806
Glaucoma, n (%)	32 (1.3)	14 (1.2)	18 (1.5)	0.531
Myopathies, n (%)	7 (0.3)	4 (0.3)	NI	0.722
Osteonecrosis of the femoral head, n (%)	NI	NI	NI	1.000

Table I. *Main demographic and clinical features of MG population, overall and stratified by gender (continuous variables presented as mean ± standard deviation and categorical variables as frequency counts and percentages, significant p values are in bold)*
CCI: Charlson Comorbidity Index; MG: myasthenia gravis; NI: not issuable (for data privacy)

	MG group (n=1,743)	Non-MG group (n=1,743)	P
A. Most frequent drugs			
Antibacterials for systemic use, n (%)	985 (56.5)	704 (40.4)	**<0.001**
Drugs for acid related disorders, n (%)	904 (51.9)	462 (26.5)	**<0.001**
Agents acting on the renin-angiotensin system, n (%)	676 (38.8)	532 (30.5)	**<0.001**
Anti-inflammatory and antirheumatic products, n (%)	609 (34.9)	486 (27.9)	**<0.001**
Other nervous system drugs, n (%)	591 (33.9)	NI	–
Antithrombotic agents, n (%)	516 (29.6)	326 (18.7)	**<0.001**
Vitamins, n (%)	459 (26.3)	205 (11.8)	**<0.001**
Lipid modifying agents, n (%)	391 (22.4)	316 (18.1)	**0.002**
Drugs for obstructive airway diseases, n (%)	356 (20.4)	228 (13.1)	**<0.001**
Beta blockers, n (%)	326 (18.7)	263 (15.1)	**0.004**
B. Most frequent causes of hospitalization			
Nervous system, n (%)	62 (3.6)	8 (0.5)	**<0.001**
Musculoskeletal system and connective tissue, n (%)	53 (3.0)	20 (1.1)	**<0.001**
Respiratory system, n (%)	52 (3.0)	9 (0.5)	**<0.001**
Digestive system, n (%)	43 (2.5)	16 (0.9)	**<0.001**
Circulatory system, n (%)	41 (2.4)	20 (1.1)	**0.007**
Eye, n (%)	30 (1.7)	–	–
Myeloproliferative DDs (poorly differentiated neoplasms), n (%)	24 (1.4)	8 (0.5)	**0.005**
Kidney and urinary tract, n (%)	20 (1.1)	–	–
Ear, nose, mouth and throat, n (%)	17 (1.0)	–	–

Table II. *Most frequent A) drug prescriptions and B) causes of hospitalization in MG vs. non-MG patients (data are shown as frequency counts and percentages, significant p values are in bold)*
DDs: diseases and disorders; MG: myasthenia gravis

A. Patients with 1 therapy (n=481 [20.3%])	
	Total, n (%)
Pyridostigmine	279 (58.0)
Corticosteroids	182 (37.8)
Thymectomy	6 (1.2)
TPE	6 (1.2)
IVIg	4 (0.8)
Immunosuppressive agents	4 (0.8)

F: 64.4 ± 15.8 vs 58.0 ± 18.5 years, p<0.001), and had a milder comorbidity profile, documented by the lower CCI (M vs F: 0.8 ± 1.3 vs 0.6 ± 1.1, p<0.001). The most common concomitant diseases were hypertension (52.4%), followed by dyslipidemia (23.3%), diabetes (14.5%), and depression (14.1%). While hypertension, dyslipidemia and diabetes showed a significantly greater proportion in male subjects (p<0.001), depression and osteoporosis were more frequently found in female patients (p<0.001) (Table I).

The clinical burden of patients with MG was compared with a control population of non-MG subjects matched for numerosity, age, sex and year of index date. Both groups, namely patients with MG and controls without MG, comprised 1,743 patients with a mean age (± SD) of 60.4 (± 16.4) years, and a proportion of 45.7% male gender. In the year before inclusion, an extensive use of drugs not related to MG was observed in patients with MG, above all antibacterials for systemic use, drugs for acid related disorders, agents acting on the renin-angiotensin system and anti-inflammatory and antirheumatic products; all the drugs analyzed were significantly more prescribed in MG group compared to the non-MG group (Table IIA).

B. Patients with 2 therapies (n=981 [41.4%])				
1st therapy	2nd therapy	Total, n (%)	Add-on, n (%)	Switch, n (%)
Pyridostigmine	Corticosteroids	535 (54.5)	405 (75.7)	130 (24.3)
Corticosteroids	Pyridostigmine	345 (35.2)	337 (97.7)	8 (2.3)
Pyridostigmine	Immunosuppressive agents	22 (2.2)	20 (90.9)	NI
Immunosuppressive agents	Pyridostigmine	20 (2.0)	20 (100)	0 (0.0)
Corticosteroids	Immunosuppressive agents	14 (1.4)	14 (100)	0 (0.0)
Immunosuppressive agents	Corticosteroids	11 (1.1)	9 (81.8)	NI
Corticosteroids	IVIg	7 (0.7)	5 (71.4)	NI
TPE	Corticosteroids	6 (0.6)	0 (0.0)	6 (100.0)
IVIg	Pyridostigmine	4 (0.4)	NI	NI
Other sequences		17 (1.7)	4 (23.5)	13 (76.5)

C. Patients with 3 therapies (n=505 [21.3%])					
1st therapy	2nd therapy	3rd therapy	Total, n (%)	Add-on, n (%)	Switch, n (%)
Corticosteroids	Pyridostigmine	Immunosuppressive agents	113 (22.4)	107 (94.7)	6 (5.3)
Pyridostigmine	Corticosteroids	Immunosuppressive agents	84 (16.6)	79 (94.0)	5 (6.0)
Pyridostigmine	Immunosuppressive agents	Corticosteroids	51 (10.1)	45 (88.2)	6 (11.8)
Immunosuppressive agents	Corticosteroids	Pyridostigmine	50 (9.9)	49 (98.0)	NI
Immunosuppressive agents	Pyridostigmine	Corticosteroids	25 (5.0)	23 (92.0)	NI
Corticosteroids	Pyridostigmine	IVIg	21 (4.2)	20 (95.2)	NI
Corticosteroids	Pyridostigmine	Thymectomy	20 (4.0)	15 (75.0)	5 (25.0)
Pyridostigmine	Corticosteroids	IVIg	19 (3.8)	16 (84.2)	NI
Pyridostigmine	Corticosteroids	Thymectomy	18 (3.6)	15 (83.3)	NI
Other sequences			104 (20.6)	77 (74.0)	27 (26.0)

Table III. *Treatment schedules in MG patients who received A) 1, B) 2 or C) 3 drug classes (data are shown as frequency counts and percentages)*

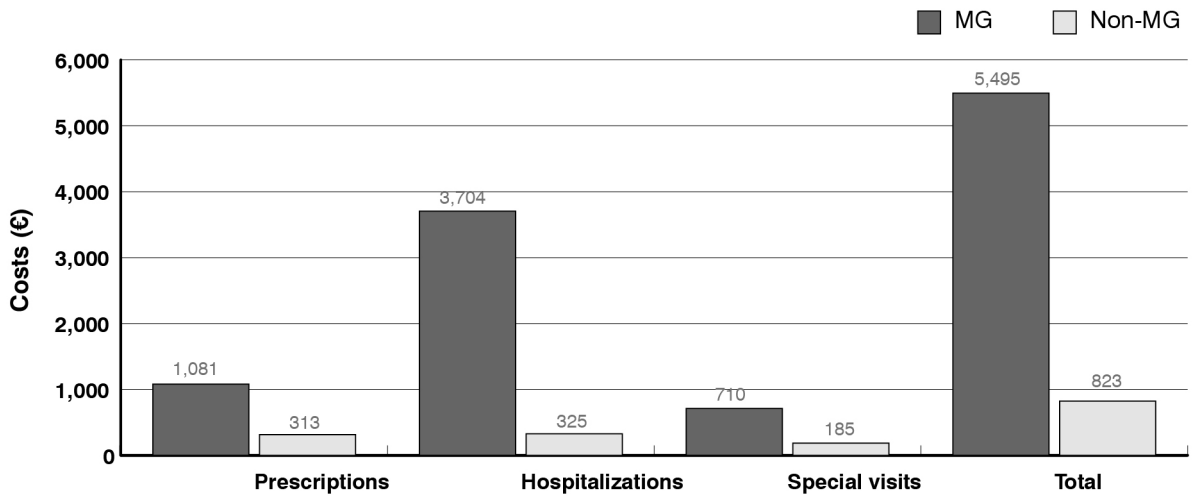
IVIg: intravenous immunoglobulins; TPE: therapeutic plasma exchange

Similarly, hospitalizations were significantly more frequent in MG patients versus non-MG subjects, regardless of the cause (Table IIB). The most common complications requiring hospital admission in MG patients were those related to nervous system (3.6%), musculoskeletal system and connective tissue (3.0%) and respiratory system (3.0%). Given that the causes of hospitalization were traced by means of the Major Diagnostic Categories (MDC) codes, the conditions related to the nervous systems (MDC1) included all the diseases / disorders of the nervous system, or cranial and peripheral nerve disorders [31].

Treatment schedules of MG

Treatment analyses were focused on adult patients only (n=2,372). More than 90% (n=2,187) of patients had at least one MG-related treatment, with pyridostigmine, corticosteroids and immunosuppressants as the mostly prescribed drugs in respectively 81.3%, 76.9% and 26.1% of patients (data not shown). Table III describes the treatment patterns in MG patients who received 1, 2 or 3 drug classes, detailing the number of treatments, the switches (change to a different therapeutic class), and the add-ons (addition of another therapeutic class). Among the MG patients included, 481 patients (20.3%) received only one treatment, in most of the cases monotherapy with either pyridostigmine (58.0%) or corticosteroids (37.8%), 981 (41.4%) received two treatments, in most of the cases (54.5%) a combination of pyridostigmine and corticosteroids, and 505 (21.3%) received three treatments, in most of the cases a combination of pyridostigmine, corticosteroids, and immunosuppressive agents (22.4%).

Among the MG patients, 185 did not receive any treatment for MG during follow-up and a focus analysis was carried out on this subset of untreated patients. The main demographic and clinical features, the comorbidities and the other treatments administered during the whole characterization in these patients are depicted in Table S1 of the Supplementary Materials. The mean age was 64.7 years, 45.9% were males and the average CCI was 1.2. The most



Major Diagnostic Category	n (%)	Cost per patient (€)
Nervous system	703 (40.3)	1,721
Respiratory system	165 (9.5)	748
Myeloproliferative DDs (poorly differentiated neoplasms)	93 (5.3)	530
Circulatory system	76 (4.4)	310
Digestive system	65 (3.7)	241
Musculoskeletal system and connective tissue	65 (3.7)	222
Blood and blood forming organs and immunological disorders	56 (3.2)	111
Hepatobiliary system and pancreas	33 (1.9)	103
Kidney and urinary tract	24 (1.4)	61

Figure 4. *Average annual direct healthcare costs per patient in MG vs non-MG group at 1-year follow-up. The detail on cost distributions by hospitalization discharge diagnosis, classified according to the MDC (Major Diagnostic Category), is also reported*

common comorbidities were hypertension (46.5%), dyslipidemia (15.7%), diabetes (15.1%), and depression (14.6%) and the most common drug prescriptions before the index-date were corticosteroids (52.4%) and pyridostigmine (39.5%). Among this 185 MG patients without MG-related drug prescriptions during follow-up, 70 (37.8%) had not received any previous therapy specific for MG either during the characterization period. The most frequent prescriptions of other medications were antibacterials for systemic use and drugs for acid related disorders at baseline, as well as after 1-year follow-up. The most common hospitalizations were due to complications involving the digestive system, musculoskeletal system and connective tissue, and respiratory system before inclusion. During the first year of follow-up the most common hospitalizations were related to nervous system and respiratory system [31].

HCRU and cost analysis

The average number of resources per patient delivered to MG group was significantly higher than in matched non-MG subjects (drug prescriptions: 21.3 ± 14.5 vs 7.9 ± 9.4, $p<0.001$; hospitalizations: 1.1 ± 1.3 vs 0.1 ± 0.4, $p<0.001$; OSS: 7.9 ± 8.0 vs 2.8 ± 5.1, $p<0.001$).

Figure 4 shows that the average annual direct healthcare costs per MG patient were equal to €5,495, markedly higher than the average cost of a non-MG patient (€823, $p<0.001$). The most impactive cost items on healthcare expenses were hospitalizations (€3,704), followed by drugs (€1,081) and outpatient services (€710). The costs for hospitalizations of MG patients were mainly driven by admissions related to nervous system (€1,721), followed by respiratory system (€748) and myeloproliferative disorders (€530).

DISCUSSION

Real-world analyses allow to observe patients in the normal clinical practice, offering the possibility of evaluating both the impact of the disease at the level of public health (through epidemiological analyses), and the "real" therapeutic management of patients in uncontrolled settings compared to those of clinical trials. Moreover, rare diseases are characterized by numerically limited populations and require a highly individualized care organization by the health services. The present real-world analysis used administrative data to provide an up-to-date epidemiology of MG in Italy together with an overview of MG therapeutic management and economic burden for the INHS.

There is growing evidence that the epidemiological numbers of MG are on the rise, up to the double compared to two decades ago, likely due to the greater incidence of MG in older patients, which in turn might be explained by the improved diagnostic tools and the increasing longevity of the global population [8]. The prevalence of MG estimated in our sample as of 31 December 2021, was around 35 cases per 100,000 people, slightly higher in females: our findings are thus consistent with the prevalence reported for other European countries, ranging from 11.2 to 36.1 per 100,000 inhabitants. These data were recently confirmed by a German analysis using a large insurance claims dataset that reported 36 prevalent MG cases per 100,000 people, a prevalence very close to our data on the Italian population [10]. Such uprising trends have been recently further corroborated by an epidemiological analysis conducted on the French National Health Data System database between 2008 and 2020, which estimated a prevalence of MG at 34.2/100,000, higher than previously reported [11]. For prevalent patients, the mean age was 58.6 years, with a larger proportion of female subjects [11]. Considering the prevalence in 2018 to exclude the possible underdiagnosed cases during the COVID-19 pandemic, we found estimates at 28.9 and 33.9 per 100,000 people for adult only and overall MG patients, respectively. These numbers are thus in line with the latest available epidemiological data on the Italian population by Antonini et al. who estimated a prevalence of MG in 2018 at 29.3 cases per 100,000 people [12].

The incidence rates of MG for year 2021 were of 4 per 100,000 subjects, thus consistent with the range of incidence of MG reported in other recent European studies (2.5 for UK, 2.9 for Sweden, around 5 in Germany, 2.5 in France [10,11,30,31] with a peak between 60-80 years. Moreover, a higher incidence among women was observed in younger age groups, while a male predominance was found from 60 years of age onwards, consistent with previous Italian reports [21]. The slight inflection of incidence rates observed in 2020 might be explained by an underdiagnosis of MG cases during the COVID-19 pandemic outbreak [26], while the peak observed in 2018 may be explained by the fact that, by end of 2017, the exemption code for MG shifted from chronic to rare diseases. As expected, over the decade 2012-2021, the mortality rates observed in MG patients were from 2 to 3 times higher compared those reported by the Italian Institute of Statistics (ISTAT) for the general population [27]. The one-year

crude mortality rate of patients assessed during 2019 to avoid possible bias for COVID-19 pandemic, confirmed that the number of deaths due to MG was increased with older age and in elderly male subjects, consistent with international reports [32,33].

Treatment schedules were found coherent with the Italian recommendation [21]: pyridostigmine was largely prescribed as entry therapy, and azathioprine was the most commonly immunosuppressant used in steroid-sparing regimens. Of note, only 20% of patients received monotherapy with either pyridostigmine or corticosteroids, while the largest majority received a combination of pyridostigmine, plus corticosteroids or a combination of pyridostigmine, corticosteroids, and immunosuppressive agents. The rates of TPE and IVIg administration were very low, whatever the number or the purpose of therapy (add-on or switch), but this might be feasibly due to the fact that these treatments are not routinely reported in the hospital discharge forms.

Unsurprisingly, compared to the age and gender-matched non-MG population, patients with MG were burdened by several comorbidities resulting in a larger consumption of drugs, not necessarily related to MG itself. This trend mirrored the data previously published by Andersen and colleagues, who reported a wider use of comedications in MG patients than in the general population [28]. Moreover, in agreement with recent evidence in Italy by Antonini et al. [12], the higher clinical complexity of MG population resulted in increased healthcare consumption and costs than in non-affected subjects. Indeed, at 1-year follow-up, the direct healthcare costs per patient found here were slightly higher compared to the previous Italian report [12], but this might be feasibly explained by the different pattern of inclusion criteria applied to select the population with MG. While in the previously published Italian analysis most of the patients were included through the criterion of pyridostigmine prescription [12], in this analysis the patients were identified through the hospitalization discharge diagnosis or the exemption code or pyridostigmine prescription. Thus, in the present analysis there might been an underestimation of the cases since MG patients only seen during outpatient visits or without exemption code were missed. Moreover, the actual prescription of immunomodulatory treatments such as plasmapheresis and intravenous immunoglobulins is underestimated since these treatment can be given to outpatients.

The principal strength of the present analysis lies in the large sample size of an unselected population in real-life settings, thus comprising patients (as elderly, or with a multimorbid profile) generally underrepresented in randomized clinical trials. Moreover, data reflected the normal clinical practice in Italy.

On the other hand, the main limitations of this analysis, which is based on data extracted from administrative flows, are related to incompleteness of clinical and laboratory data (i.e. antibody status and disease severity) and of non-measurable variables including patient attitude towards medication, and the use of out-of-pocket drugs not traceable in the databases. The therapeutic pattern may be affected by the inclusion criteria applied (i.e., presence of pyridostigmine) as well as the study period, which did not allow to collect data on the most recent therapeutic options for MG if they were not reimbursed yet at the time of the analysis. Besides, it was not possible to discern whether some medications like corticosteroids or immunosuppressants were actually prescribed for MG itself or concomitant conditions. Moreover, exemption flow might be incomplete as not all subjects with MG have an exemption code: in fact, 496 (77.1%) of 643 patients without exemption for MG or other pathology, had at least one hospitalization for MG. In addition, given that the inclusion criteria were based on MG hospitalization discharge diagnosis or MG active exemption code or pyridostigmine prescription, MG patients seen during outpatient visits or without exemption code might have been missed, resulting in an underestimation of MG cases. Furthermore, MG itself and the comorbidities were detected using hospital discharge codes, exemption codes and drug prescriptions as proxy of diagnosis, so it was not possible to establish disease severity nor to discriminate between ocular and generalized MG. Regarding cost analysis, the hospitalization database and the DRG system do not accurately detect the cost for the pathology, for a number of reasons. First, it is by no means certain that all treatments and diagnoses are fully reported into the hospital discharge forms; secondly, some more expensive therapies, such as TPE and IVIg, might not be entered and therefore not traced, thus explaining the apparently low prescription of immunomodulatory treatments in our cohort.

CONCLUSIONS

This real-world analysis provided up-to-date picture on MG patients in Italy. The incidence and prevalence of MG in Italy was in general aligned with other European countries.

Our data confirmed the high clinical and economic burden of disease: MG population displayed a large drug utilization, especially pyridostigmine and corticosteroids, and a clinical profile burdened by several comorbidities with potentially relevant repercussions of patients' quality of life. This resulted in healthcare costs associated with MG patients about 6-times higher compared to subjects without the disease, suggesting that further efforts are still needed to optimize the therapeutic management of these patients and to reduce national healthcare expenditures from the INHS perspective.

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Conflicts of interest
The authors declare that they have no competing interests or personal related to the present manuscript.

Ethical standards
The study involving was reviewed and approved by the local Ethics Committee of the participating healthcare entities and has therefore been performed in accordance with the ethical standards.
Patients' informed consents were not collected based on the pronouncement of the Data Privacy Guarantor Authority (General Authorization for personal data treatment for scientific research purposes—n.9/11 December 2014—published on the Official Gazette n. 301 on 30 December 2014), which authorizes data treatment without informed consent when collection is impossible due to organizational reasons.

Data availability
All data used for the current study are available upon reasonable request to CliCon S.r.l., which is the body entitled to data treatment and analysis by participating Local Health units.

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