Economic Costs of Myasthenia Gravis: A Systematic Review

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Abstract

Objectives The objective of our study was to conduct a systematic literature review of economic costs (henceforth costs) associated with myasthenia gravis (MG).

Methods We searched MEDLINE (through PubMed), CINAHL, Embase, PsycINFO, and Web of Science for studies reporting costs of MG published from inception up until March 18, 2020, without language restrictions. Two reviewers independently screened records for eligibility, extracted the data, and assessed included studies for risk of bias using the Newcastle–Ottawa Scale. Costs were inflated and converted to 2018 United States dollars ($).

Results The search identified 16 articles for data extraction and synthesis. Estimates of costs of MG were found for samples from eight countries spanning four continents (Europe, North America, South America, and Asia). Across studies, the mean per-patient annual direct medical cost of illness was estimated at between $760 and $28,780, and cost per hospitalization between $2550 and $164,730. The indirect cost of illness was estimated at $80 and $3550. Costs varied considerably by patient characteristics, and drivers of the direct medical cost of illness included intravenous immunoglobulin and plasma exchange, myasthenic crisis, mechanical ventilatory support, and hospitalizations.

Conclusions We show that the current body of literature of costs of MG is sparse, limited to a few geographical settings and resource categories, mostly dated, and subject to non-trivial variability, both within and between countries. Our synthesis will help researchers and decision-makers identify gaps in the local health economic context of MG and inform future cost studies and economic evaluations in this patient population.

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Key Points for Decision Makers

To our knowledge, no study has systematically reviewed the literature for costs associated with myasthenia gravis (MG).

The body of literature of costs of MG is sparse, limited to a few geographical settings and resource categories, mostly dated, and subject to non-trivial variability.

Our synthesis will help researchers and decision-makers identify gaps in the local health economic context of MG and inform future cost studies and economic evaluations in this patient population.

1 Introduction

Myasthenia gravis (MG) is an autoimmune disease in which antibodies react with structures of the neuromuscular junction, leading to impairment or failure of neuromuscular transmission [1]. Clinically, the disease results
in problems with vision, fatigable weakness, swallowing difficulties, and loss of ambulation, but may prove fatal following myasthenic crisis (i.e. paralysis of the respiratory muscles) in the absence of appropriate interventions. Acetylcholinesterase inhibitors may be sufficient to manage the mildest presentations of MG, but generalized forms usually require long-term treatment with corticosteroids and immunosuppressants, thymectomy, intravenous immunoglobulin (IVIG), or plasma exchange (PLEX) [2]. However, for a considerable proportion of MG patients, these generalized treatments lack effectiveness and/or are accompanied by non-trivial side effects [3].

In recent decades, promising treatment strategies, including immunomodulation with specific monoclonal antibodies (“biologics”), have been explored for MG, and several clinical trials involving humans have just been completed or are still in progress [4]. Given the growing arsenal of therapy choices available to MG clinicians, there is an emerging body of literature studying the health economics of MG that has previously not been systematically reviewed. The objective of our study was to conduct a systematic review of economic costs (henceforth costs) of MG globally. Specifically, this systematic literature review sought to answer the following questions:

- In which geographical settings have costs of MG been studied?
- What types of costs have been estimated in patients with MG?
- What are the known costs of MG?

2 Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [5].

2.1 Search Strategy and Selection Criteria

We searched MEDLINE (through PubMed), CINAHL, Embase, PsycINFO, and Web of Science for full-text records of studies reporting costs of MG published from inception up until March 18, 2020, without language restrictions. The search string contained a combination of the following medical subject heading terms, title/abstract, and topic field tags: “myasthenia gravis”, “cost”, “financial”, “burden”, “economic”, “monetary”, “cost of illness”, “costs and cost analysis”, “cost–benefit analysis”, “cost-effectiveness”, and “cost-utility” (full search strings available in the “Appendix”—see the electronic supplementary material). We included all identified publications reporting costs of MG in any currency. We excluded studies based on samples comprising fewer than ten patients (to allow for meaningful inference), and also required that results were reported separately for patients with MG. No further criteria were imposed for study eligibility.

2.2 Screening, Data Extraction, and Assessment of Risk of Bias

Two independent investigators (EL and OP) initially screened article titles and abstracts for eligibility, and subsequently reviewed full-text versions of selected records. The reasons for article exclusion were recorded and disagreements were resolved by the involvement of a third investigator (HL). For all articles included in the review, the following data were extracted: author, year, setting, design, data sources, type of data, study periods, patient population, estimated costs, and cost result. For studies reporting costs for multiple time periods, we only extracted the most recent data, and we only considered estimates for subgroups comprising ten or more patients. We did not extract costs of individual resources (e.g. the cost of a specific medicine or a visit to a general practitioner) reported as part of higher-level cost categories (e.g. the direct medical cost of illness).

Result data from each article were synthesized and reported with respect to the three review questions as stated in the Sect. 1. We sought (when feasible) to structure identified estimates into the following commonly examined cost categories (based on the information in the reviewed publications): direct medical cost (i.e. the opportunity cost of medical resources directly included in the formal management of the disease), direct non-medical cost (i.e. the opportunity cost of non-medical resources directly included in the formal management of the disease), informal care cost (i.e. the opportunity cost of non-medical resources directly included in the informal management of the disease), and indirect cost (typically quantified as production losses from the perspective of society due to absenteeism and presenteeism from work [6]). To facilitate comparison, identified cost estimates were inflated to 2018 values using country-specific consumer price index data from the World Bank [7] and subsequently converted to United States (US) dollars ($) using the following rates: Colombian peso COL$1 = $0.00030; Canadian dollar C$1 = $0.747; New Taiwan dollar NT$1 = $0.032; Yen ¥1 = $0.009; Euro (German) €1 = $1.130; Indian rupee ₹1 = $0.014; and Thai baht ฿1 = $0.033. All reported cost estimates, extracted or derived, were rounded to the nearest ten.
Risk of bias was established with the Newcastle–Ottawa Scale (NOS) [8]. The NOS was developed to assess the quality and risk of bias of non-randomized studies in three dimensions: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. Each category is attributed a score rating (maximum score: ◊◊◊◊ for selection, ◊◊ for comparability, and ◊◊◊ for outcome). To ascertain selection, we required patients to be diagnosed with MG, that the diagnosis was confirmed via International Statistical Classification of Diseases and Related Health Problems (ICD) codes (e.g. ICD-9 358.00 and ICD-10 G70.0) in an out- or inpatient setting, and that the sample was not restricted in terms of level of fatigable weakness (or other markers limiting representativeness) (assessment of non-exposed was not applicable); to ascertain comparability, we required details of the distribution of age and sex in the sample population, as well as MG crisis/exacerbation (as applicable); and to ascertain outcome, we required that the data were extracted from clinical charts, registries, or databases (i.e. not patient self-reported, per the scale manual), there was a minimal follow-up of 1 month for prospective studies (given the frequency of care reported), and < 25% of the total sample were lost to follow-up during the study period.

3 Results

The systematic review resulted in the identification of 848 publications (Fig. 1). Of these, 274 were duplicates, 543 were excluded following title and abstract screening, and 31 were selected for full-text review. Finally, 16 articles [9–24] were considered for data extraction and synthesis. Summary details of the included publications are presented in Table 1.
| Author (year)            | Setting          | Design                                      | Data source(s)                  | Type of data                              | Study period(s) | Patient population                                                                 |
|-------------------------|------------------|---------------------------------------------|----------------------------------|-------------------------------------------|-----------------|-------------------------------------------------------------------------------------|
| Chicaiza-Becerra et al. (2012) [9] | Colombia         | Modelling study (CEA)                       | Published literature             | Clinical and economic model input data    | NR              | Patients with MG not associated with thymoma (n and distribution of age and sex NR) |
| Desai et al. (2020) [23] | The United States | Retrospective, observational cohort study    | The NIS part of the HCUP Claims data | Claims data                              | 2007–2014       | 175 patients with takotsubo syndrome secondary to MG crisis (median age: 73 years; 80% female) |
| Furlan et al. (2016) [10] | Canada           | Retrospective, observational cohort study; modelling study (CMA) | RCT; the Toronto General Hospital (Ontario, Canada); local unit costs | RCT, hospital expense, and unit cost model input data | 2007–2010       | 38 adults with MG treated with IVIG (mean age: 60 years; 55% female) and 32 with PLEX (mean age: 58 years; 53% female) for exacerbation of moderate to severe MG |
| Guptill et al. (2011) [11] | The United States | Retrospective, observational cohort study | The AHS disease management database | Claims data                              | 2008–2010       | 1288 children and adults with MG (mean age: 60 years; 59% female)                   |
| Guptill et al. (2012) [12] | The United States | Retrospective, observational cohort study | The AHS disease management database | Claims data                              | 2009            | 113 children and adults with MG (mean age: 60 years; 59% female)                   |
| Heatwole et al. (2011) [13] | The United States | Modelling study (CMA)                       | Published literature; national unit costs | Clinical and economic model input data | NR              | Patients with MG crisis (n and distribution of age and sex NR)                      |
| Lai and Tseng (2010) [14] | Taiwan           | Retrospective, observational cohort study   | The NHIRD                        | Claims data                              | 2000–2007       | 5211 children and adults with MG (distribution of age and sex NR) receiving therapeutic and surgical treatment |
| Mandawat et al. (2010) [15] | The United States | Retrospective, observational cohort study   | The NIS part of the HCUP Claims data | Claims data                              | 2000–2005       | 1606 patients hospitalized for MG or MG crisis treated with IVIG or PLEX (distribution of age and sex for each stratum reported in the article) |
| Mouri et al. (2019) [16]  | Japan            | Retrospective, observational cohort study   | The Japanese Diagnosis Procedure Combination database | Claims data                              | 2010–2016       | 795 adults with MG hospitalized to receive thymectomy under general anaesthesia also treated with sugammadex (mean age: 55 years; 54% female) or placebo (mean age: 54 years; 50% female) |
AHS The Accordant Health Services, CEA cost-effectiveness analysis, CMA cost-minimization analysis, HCUP Healthcare Cost and Utilization Project, IVIG intravenous immunoglobulin, JMDC Japan Medical Data Center, MG myasthenia gravis, NHIRD National Health Insurance Research Database, NIS National (Nationwide) Inpatient Sample, NR not reported, PLEX plasma exchange, RCT randomized controlled trial

| Author (year)            | Setting            | Design                        | Data source(s)                          | Type of data  | Study period(s) | Patient population                                                                 |
|--------------------------|--------------------|-------------------------------|-----------------------------------------|---------------|-----------------|-------------------------------------------------------------------------------------|
| Narla et al. (2020) [24] | The United States  | Retrospective, observational cohort study | The NIS part of the HCUP                | Claims data   | 2002–2012       | Patients with MG with pemphigus or pemphigoid (n and distribution of age and sex NR) |
| Ogino et al. (2017) [17] | Japan              | Retrospective, observational cohort study | The JMDC                                 | Claims data   | 2015–2016       | Patients with MG (n and distribution of age and sex NR)                              |
| Omorodion et al. (2017) [18] | The United States  | Retrospective, observational cohort study | The NIS part of the HCUP                | Claims data   | 2003–2013       | 6394 children and adults hospitalized for MG exacerbation and discharged alive (results stratified by age categories; 58% female) |
| Schepelmann et al. (2010) [19] | Germany       | Cross-sectional, observational study | Survey administrated to patients identified via specialized centres part of the German Network of Muscle Disorders; national unit costs | Self-reported data | 2005            | 41 adults with MG (mean age NR; 56% female)                                           |
| Sonkar et al. (2017) [20] | India             | Prospective, observational cohort study | Tertiary care teaching hospital in India | Self-reported and hospital expense data | 2014–2016       | 66 children and adults with MG (median age 42 years; 41% female) receiving conventional therapy and surgery (thymectomy) |
| Souayah et al. (2009) [21] | The United States  | Retrospective, observational cohort study | The NIS part of the HCUP                | Claims data   | 2001–2002       | 994 patients with severe MG with a primary or secondary procedure code for continuous mechanical ventilation (mean age: 65 years; 53% female) |
| Tiamkao et al. (2014) [22] | Thailand          | Retrospective, observational cohort study | The National Health Security Office (Bangkok, Thailand) | Claims data   | 2009–2010       | 936 adult patients with MG (mean age: 45 years; 72% female)                           |
Most articles (75%, 12 of 16) described results from retrospective, observational cohort research, and 31% (five of 16) were based on publicly accessible data from the National (Nationwide) Inpatient Sample (NIS) part of the Healthcare Cost and Utilization Project (HCUP) in the US.

3.1 In Which Geographical Settings have Costs of MG Been Studied?

Estimates of costs of MG were found for samples from a total of eight countries across four continents (Europe, North America, South America, and Asia) (Table 1). In total, 50% (eight of 16) represented research in patients from the US [11–13, 15, 18, 21, 23, 24].

3.2 What Types of Costs have been Estimated for Patients with MG?

In total, six of 16 (38%) of identified articles estimated the direct medical costs of MG [11, 12, 14, 17, 19, 20], seven of 16 (44%) estimated cost per hospitalization [14, 16, 18, 21–24], three of 16 (19%) estimated costs of IVIG and PLEX as a treatment for MG crisis/exacerbation [10, 13, 15], two of 16 (13%) estimated indirect costs [19, 20], and one of 16 (6%) estimated costs of myasthenic crisis [9], cost per MG outpatient care service [14], and total cost of illness [19], respectively (Table 1). Schepelmann et al. [19] also estimated informal care costs of MG in Germany, accounted for as an indirect cost of illness.

3.3 What are the Known Costs of MG?

Identified costs of MG reported by the included studies are presented in Table 2. Estimates of the mean per-patient annual direct medical cost of illness ranged from $760 in Japan [17] to $28,780 in the US [11]. In addition, Sonkar et al. [20] estimated the median per-patient annual direct medical cost (quantified as out-of-pocket expenditures due to the lack of national healthcare insurance) in India at $730. However, there was some variability across studies concerning included medical resources (Table 3). Two studies [19, 20] considered transportation costs, typically accounted for as a direct non-medical cost, in their calculation of direct medical cost of illness, and one [19] also included costs associated with home equipment. Guptill et al. [11] found the mean per-patient annual direct medical cost of illness in the US to vary by age, ranging from $9100 in patients 0–19 years of age to $23,820 in those older than 65 years.

Main drivers of the direct medical cost of illness were IVIG [11, 20] and PLEX [20], as well as myasthenic crisis [20], mechanical ventilatory support [20], and hospitalizations [12, 20]. Costs appear to also be driven by very high healthcare utilization in some patient groups. For example, Guptill et al. [11] reported that the subset of US patients who received more than 20 infusions of IVIG in the 2-year study period (determined from the health plan payments) accounted for 62% of all MG-related pharmacy costs.

Estimates of the mean per-patient cost per hospitalization, all based on claims data, ranged between $2550 and $164,730 (in 2018 US dollars) (Table 2). The lowest estimate was derived from a sample of 936 Thai patients hospitalized for MG [22], and the highest for 994 US patients hospitalized for MG requiring continuous mechanical ventilation [21]. In relation to all US hospital admission that calendar year, Omorodion et al. [18] estimated the mean per-patient added cost per hospitalization for MG exacerbation in the US in 2013 at $59,340 ($98,800 vs. $39,460). Looking into results from reported subgroup analyses, Omorodion et al. [18] found costs per hospitalization to be higher for males compared with females hospitalized for MG exacerbation ($119,100 vs. $97,330) and in the West of the US compared with the Midwest ($55,850 vs. $34,560), whereas Souayah et al. [21] reported higher costs for urban non-teaching compared with teaching hospitals ($165,150 vs. $104,980), and both recognized that the mean per-patient cost per hospitalization varied markedly by age (Table 2).

The mean per-patient indirect cost of MG was estimated at $80 and $3550 (Table 2). The former was based on self-reported data from 66 Indian patients and their caregivers and included production losses due to absenteeism and presenteeism estimated by valuing the number of lost work days, as well as time lost for patients and caregivers, at the daily wage, and subsequently adding caregivers’ expenditure for travel, food, and stay while in the hospital [20]. In contrast, the latter estimate, based on self-reported data from 41 German patients and their caregivers, included production losses due to premature retirement and temporary sickness estimated in patients <65 years of age by valuing the number of lost work days at the daily wage, as well as estimates of informal care (defined as home care provided by family and friends) calculated by valuing the number of hours of informal care with the daily wage [19].

The mean per-patient cost of IVIG as a treatment for MG crisis/exacerbation was estimated at $6620 in Canada [10] (including hospital costs, costs of blood products, and physician fees) and $90,760 [13] in the US (including cost of therapy, cost of hospitalization, and cost of secondary complications). Corresponding estimates for PLEX were $4990 [10] and $116,470 [13], respectively. In addition, Mandawat et al. [15] estimated the median per-patient hospital cost (reflecting total hospital charges) of IVIG and PLEX in the US at $28,080 and $35,450 in patients with MG, and $94,900 and $70,170 in those with MG crisis.

The mean per-patient total cost of illness, including direct medical, informal care, and indirect costs, was estimated...
| Author (year) | Estimated cost(s)                                                                 | Perspective of analysis | Currency; year of valuation | Cost result(s) [in 2018 US dollars]§ | Risk of bias† |
|--------------|----------------------------------------------------------------------------------|-------------------------|------------------------------|--------------------------------------|---------------|
| Chicaiza-Becerra et al. (2012) [9] | Cost of MG crisis (including medical treatment and inpatient care) | Healthcare/payer         | Colombian peso (COLS); 2008  | Mean per-patient cost of myasthenic crisis (n=NR): COLS10,360 [< $10] | Selection: ◊◊◊◊ Comparability: ◊ (age and sex NR) Outcome: ◊ ◊ |
| Desai et al. (2020) [23] | Cost per hospitalization of takotsubo syndrome secondary to MG crisis (i.e. total hospital charge) | Healthcare/payer         | US dollar ($) ; year NR        | Median per-patient cost per hospitalization (n = 175): $134,000 [142,130] | Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊ ◊ |
| Furlan et al. (2016) [10] | Cost of IVIG and PLEX (including hospital costs, costs of blood products, and physician fees) as treatment for exacerbation of moderate to severe MG | Healthcare/payer         | Canadian dollar (CS); 2014    | Mean per-patient cost of IVIG (n = 32): C$8310 [$6620] | Selection: ◊◊◊◊ Comparability: ◊ Outcome: ◊ ◊ |
| Guptill et al. (2011) [11] | Direct medical cost                                                             | Healthcare/payer         | US dollar ($) ; year NR        | Mean per-patient annual direct medical cost (pooled sample, n = 1288): $24,990 [$28,780] | Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊ ◊ |
| Guptill et al. (2012) [12] | Direct medical cost                                                             | Healthcare/payer         | US dollar ($) ; year NR        | Mean per-patient annual direct medical cost (age: 0–19 years, n = 21): $7910 [$9100] | Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊ ◊ |
| Heatwole et al. (2011) [13] | Cost of IVIG and PLEX (including cost of therapy, cost of hospitalization, and cost of secondary complications) as a treatment for MG crisis | Healthcare/payer         | US dollar ($) ; year NR        | Mean per-patient annual direct medical cost (age: 20–39 years, n = 84): $37,520 [$43,210] | Selection: ◊◊◊◊ Comparability: ◊ Outcome: ◊ ◊ |
| Lai and Tseng (2010) [14]  | Direct medical cost; cost per outpatient care service; cost per hospitalization | Healthcare/payer         | New Taiwan dollar (NTS); 2007 | Mean per-patient direct medical cost (n = 3205): NTS42,080 [$1780] | Selection: ◊◊◊◊ Comparability: ◊ (age and sex NR) Outcome: ◊ ◊ |
| Author (year)          | Estimated cost(s)                                                                 | Perspective of analysis | Currency; year of valuation | Cost result(s) [in 2018 US dollars] | Risk of bias† |
|-----------------------|-----------------------------------------------------------------------------------|-------------------------|------------------------------|-------------------------------------|---------------|
| Mandawat et al. (2010) [15] | Hospital cost (i.e. total hospital charge) of IVIG and PLEX as treatment for MG and MG crisis, respectively | Healthcare/payer        | US dollar ($); year NR        | Median per-patient hospital cost of IVIG (MG, n = 171): $21,120 [$28,080] | Selection: ◊◊◊◊ |
|                       |                                                                                   |                         |                              | Median per-patient hospital cost of PLEX (MG, n = 737): $26,660 [$35,450] | Comparability: ◊ |
|                       |                                                                                   |                         |                              | Median per-patient hospital cost of IVIG (MG crisis, n = 169): $33,920 [$45,100] | Outcome: ◊◊   |
|                       |                                                                                   |                         |                              | Median per-patient hospital cost of PLEX (MG crisis, n = 529): $53,800 [$71,520] |               |
| Mouri et al. (2019) [16] | Cost per hospitalization (i.e. total hospital charge)                            | Healthcare/payer        | US dollar ($); year NR        | Median per-patient cost per hospitalization (sugammadex, n = 506): $13,190 [$13,800] | Selection: ◊◊◊◊ |
|                       |                                                                                   |                         |                              | Median per-patient cost per hospitalization (placebo, n = 289): $14,120 [$14,770] | Comparability: ◊ |
|                       |                                                                                   |                         |                              |                                                                                     | Outcome: ◊◊    |
| Narla et al. (2020) [24] | Cost per hospitalization (derived from hospital charges using the cost-to-charge ratio from the HCUP) | Healthcare/payer        | US dollar ($); 2014           | Mean (geometric) per-patient cost per hospitalization (pemphigus, n = NR): $14,970 [$15,880] | Selection: ◊◊◊◊ |
|                       |                                                                                   |                         |                              | Mean (geometric) per-patient cost per hospitalization (pemphigoid, n = NR): $13,300 [$14,110] | Comparability: ◊ (age and sex NR) |
|                       |                                                                                   |                         |                              |                                                                                     | Outcome: ◊◊    |
| Ogino et al. (2017) [17] | Direct medical cost                                                               | Healthcare/payer        | Yen (¥); 2016                 | Mean per-patient annual direct medical cost (n = NR): ¥82,940 [$760] | Selection: ◊◊◊◊ |
|                       |                                                                                   |                         |                              |                                                                                     | Comparability: ◊ (age and sex NR) |
|                       |                                                                                   |                         |                              |                                                                                     | Outcome: ◊◊    |
| Author (year) | Estimated cost(s)                                                                 | Perspective of analysis | Currency; year of valuation | Cost result(s) [in 2018 US dollars§]                                                                 | Risk of bias† |
|--------------|----------------------------------------------------------------------------------|-------------------------|-----------------------------|---------------------------------------------------------------------------------------------------|---------------|
| Omorodion et al. (2017) [18] | Cost per hospitalization (i.e. total hospital charge) | Healthcare/payer | US dollar ($) ; 2013 | Mean per-patient cost per hospitalization (pooled sample, \( n = 5535 \)): $98,800 [$106,490] Mean per-patient cost per hospitalization (age: 1–7 years, \( n = 145 \)): $66,860 [$72,070] Mean per-patient cost per hospitalization (age: 18–44 years, \( n = 1195 \)): $82,790 [$89,240] Mean per-patient cost per hospitalization (age: 45–64 years, \( n = 1705 \)): $93,030 [$100,280] Mean per-patient cost per hospitalization (age: 65–84 years, \( n = 1705 \)): $117,000 [$126,110] Mean per-patient cost per hospitalization (age: ≥ 85 years, \( n = 320 \)): $83,710 [$90,240] Mean per-patient cost per hospitalization (males, \( n = 2380 \)): $110,490 [$119,100] Mean per-patient cost per hospitalization (females, \( n = 3150 \)): $90,290 [$97,330] | Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊ |
| Schepelmann et al. (2010) [19] | Direct medical cost; indirect cost (production losses due to absenteeism and presenteeism, as well as informal care, estimated using the HCA); and total cost of illness | Societal | Euro (€); 2009 | Mean per-patient annual direct medical cost (\( n = 41 \)): €11,840 [$15,050] Mean per-patient annual indirect cost (including informal care) (\( n = 41 \)): €2790 [$3550] Mean per-patient annual informal care cost (\( n = 41 \)): €910 [$1160] Mean per-patient annual total cost of illness (\( n = 41 \)): €14,950 [$19,000] Mean per-patient annual total cost of illness (ADL assistance, \( n = NR \)): €44,690 [$56,800] Mean per-patient annual total cost of illness (no ADL assistance, \( n = NR \)): €11,360 [$14,440] | Selection: ◊◊◊◊ Comparability: ◊◊ Outcome: ◊◊ (self-reported data) |
Table 2 (continued)

| Author (year) | Estimated cost(s)                                                                 | Perspective of analysis | Currency; year of valuation | Cost result(s) [in 2018 US dollars§]                          | Risk of bias† |
|---------------|----------------------------------------------------------------------------------|-------------------------|-----------------------------|----------------------------------------------------------------|--------------|
| Sonkar et al. (2017) [20] | Direct medical cost (i.e. out-of-pocket expenditures incurred during the management of MG and associated co-morbidities\(^{3}\)); indirect cost (i.e. production losses due to absenteeism and presenteeism) estimated using the HCA\(^{2}\) | Societal                | Indian rupee (₹); 2016    | Median per-patient annual direct medical cost (\(n = 66\)): ₹48,570 [$730]  
Median per-patient annual indirect cost (\(n = 66\)): ₹5,100 [$80]  
Median per-patient annual total cost of illness (\(n = 66\)): ₹61,390 [$920] | Selection: ◊◊◊◊  
Comparability: ◊  
Outcome: ◊◊ (self-reported data) |
| Souayah et al. (2009) [21] | Cost per hospitalization (i.e. total hospital charge)                              | Healthcare/payer        | US dollar ($) ; 2002        | Mean per-patient cost per hospitalization (pooled sample, \(n = 994\)): $118,000 [$164,730]  
Mean per-patient cost per hospitalization (age: < 50 years, \(n = 196\)): $113,100 [$157,890]  
Mean per-patient cost per hospitalization (age: ≥ 50 years, \(n = 798\)): $119,100 [$166,260]  
Mean per-patient cost per hospitalization (urban teaching hospital, \(n = NR\)): $75,200 [$104,980]  
Mean per-patient cost per hospitalization (urban non-teaching hospital, \(n = NR\)): $118,300 [$165,150] | Selection: ◊◊◊◊  
Comparability: ◊  
Outcome: ◊◊◊ |
| Tiamkao et al. (2014) [22] | Cost per hospitalization (i.e. total hospital charge)                              | Healthcare/payer        | Thai baht (฿); 2010         | Mean per-patient cost per hospitalization (\(n = 936\)): ฿68,730 [$2550] | Selection: ◊◊◊◊  
Comparability: ◊  
Outcome: ◊◊ |

Costs were rounded to the nearest ten

Details of resources included in estimates of direct medical costs are presented in Table 3

ADL activities of daily living, HCA human capital approach, HCUP Healthcare Cost and Utilization Project, IVIG intravenous immunoglobulin, MG myasthenia gravis, NR not reported, PLEX plasma exchange

\(^{1}\)Converted to United States (US) dollars ($) [Colombian peso COLS\(1 = $0.00030\); Canadian dollar C\(S1 = $0.747\); New Taiwan dollar NT\(S1 = $0.032\); Yen ¥1 = $0.009; Euro (German) €1 = $1.130; Indian rupee ₹\(1 = $0.014\); and Thai baht ฿1 = $0.033] and inflated to 2018 values using consumer price index data from the World Bank [7]

\(^{2}\)Assessed with the Newcastle–Ottawa Scale. Maximum score: ◊◊◊◊ for selection, ◊◊ for comparability, and ◊◊◊ for outcome (see “Methods” section for details)

\(^{3}\)In the absence of data, year of valuation was assumed to be 2014

\(^{4}\)In the absence of data, year of valuation was assumed to be 2010

\(^{5}\)In the absence of data, year of valuation was assumed to be 2009

\(^{6}\)In the absence of data, year of valuation was assumed to be 2005

\(^{7}\)In the absence of data, year of valuation was assumed to be 2016

\(^{8}\)Including costs of transportation to the hospital, subsequent hospitalization, over-the-counter medications, laboratory tests, and the food consumed during the waiting period

\(^{9}\)Indirect cost of illness also included time lost for the patient and caregivers (valued at the daily wage), as well as caregivers' expenditure for travel, food, and stay while in hospital
at $19,000 in Germany [19]. Patients who required assistance with activities of daily living were found to have significantly higher costs than those who did not ($56,800 vs. $14,440), and there was a trend of higher costs for older patient groups. Additional details of identified costs are presented in Table 2.

In total, 56% (nine of 16) of included studies were judged to have low risk of bias as assessed using the NOS (see Table 1). Reasons for increased risk of bias included limited comparability due to inadequate description of the distribution of age and sex in the studied samples [9, 13, 14, 17, 20, 24], and self-reported data [19, 20].

### 4 Discussion

In this study, we systematically reviewed the literature for estimates of costs associated with MG. Our findings, spanning eight countries across four continents, show that specific components of the cost burden are relatively well-described in some settings (e.g. the direct medical cost in the US), but also reveal that up-to-date data are lacking for many resource categories and countries. Our synthesis of data also demonstrates that resource use and accompanying costs associated with MG appear to be sensitive to geographic variation in healthcare systems, as well as the medical management of the disease. This is true both within and between countries. We also noted that costs depend heavily on demographic and clinical characteristics of the underlying patient populations.

We identified six estimates of the mean per-patient annual direct medical cost of illness of MG. As expected, due to differences in the organization, provision, and utilization of healthcare and currency purchasing power (among other factors), costs for the US ($28,780 [11] and $23,630 [12]) were notably higher than estimates derived from samples from India ($730) [20] and Taiwan ($1780) [14], but also Germany ($15,050) [19] and in particular Japan ($760) [17]. One reason for this heterogeneity, in addition to actual differences across countries in the medical management of MG, includes variability in resources included in the analysis (as illustrated in Table 3). For example, US estimates included parts of costs associated with IVIG and PLEX (which have, in a separate US study [15], been estimated at $28,080 and $35,450 in patients with MG, respectively), whereas the Japanese study did not. In addition, it is worth noting that, according to the Organisation for Economic Co-operation and Development (OECD) [25], purchasing power parity-adjusted health expenditure per capita is more than twice as large in the US compared with Japan. Observed differences in costs could also be a function of the employed perspective of analysis (e.g. healthcare/payer vs. societal) and valuation of included resources. Interestingly, to further analyse the added direct medical costs associated with MG in the US, Gupta et al. [12] included a matched control group comprising non-MG members of the general population. The mean per-patient annual cost attributable to the medical management of MG was $15,680 ($18,350 in 2018 values), making up 78% of the total direct medical cost recorded. This indicates that MG typically dominates over other medical co-morbidities, as costs associated with the disease formed the majority of healthcare expenditures.

Our review also shows that published data of the mean per-patient cost per hospitalization vary substantially across studies, settings, and sample characteristics. Similar to estimates of direct medical costs, this variability is due to inter-study differences pertaining to the disease severity and morbidity profile of the hospitalized patients, the inpatient care of MG, and included resources and their valuation, among other factors. Although not part of the data extraction, two studies reported that costs cost per hospitalization associated with MG had risen over time in the US. Souayah et al. [21] found that the mean charge for patients hospitalized for MG requiring continuous mechanical ventilation had

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**Table 3** Resources included in identified estimates of the direct medical cost of MG

| Author (year) | Inpatient care | Outpatient care | Prescription drugs | OTC drugs | IVIG/PLEX | Co-payments |
|---------------|----------------|-----------------|--------------------|-----------|-----------|-------------|
| Ogino et al. (2017) [17] | × | × | × | NR | | |
| Sonkar et al. (2017) [20] | × | × | × | × | × | NA² |
| Gupta et al. (2011) [11] | × | × | × | × | × | × |
| Gupta et al. (2012) [12] | × | × | × | × | × | × |
| Lai et al. and Tseng (2010) [14] | × | × | | NR | | |
| Schepelmann et al. (2010) [19] | × | × | × | NR | NR | × |

*IVIG intravenous immunoglobulin, MG myasthenia gravis, NA not applicable, NR not reported (i.e. the information was not provided, but the specific resource category could have been included in the estimation, for example, as part of higher level cost categories), OTC over-the-counter, PLEX plasma exchange

²The direct medical cost was estimated based on patients’ out-of-pocket expenditure

²Excluding inpatient IVIG costs
increased by 40% ($84,100 vs. $118,000) from 1991–1992 to 2001–2002. However, the increase was only seen in patients admitted to urban non-teaching hospitals. Conversely, for urban teaching hospitals, total charges during the same 10-year period decreased. Given the data in the article, it is not possible to directly investigate reasons for this development. The second study [18] that examined costs over time found that the total mean per-patient charge per hospital admission for MG exacerbation in the US increased by 135% ($48,020 vs. $98,800) from 2003 to 2013. The authors suggest that this increase might be attributed to changes in the underlying practice pattern of the disease, a rise in the prevalence of MG among the elderly (a subpopulation that on average has higher resource needs and costs compared with younger individuals), and/or increased utilization and costs of IVIG and PLEX over time. Interestingly, in the same study, the mean per-patient cost per hospitalization of multiple sclerosis also rose by an almost identical proportion (106%) from 2003 to 2013 [18], indicating that the increase may be related to more general (non-disease-specific) factors within the healthcare system.

We identified a total of four studies that reported stratified cost estimates by patient age and/or disease status/severity. Guptill et al. [11] found that patients incurred the highest total direct medical costs during their second and third decade of life (possibly due to a higher frequency of thymectomy and/or non-steroidal immunosuppressive agents in this age group, according to the authors). In contrast, Omorodion et al. [18] found that the mean cost per hospitalization was highest in the oldest patients (i.e. 65–84 years of age), in line with findings reported by Souayah et al. [21] for patients ≥ 50 years of age versus < 50 years (Table 2). Finally, Schepelmann et al. [19] estimated the mean per-patient annual total cost of illness in patients requiring assistance with activities of daily living at $56,800, markedly higher than estimates for those without assistance ($14,440). This surprisingly wide range in costs is indicative of the heterogeneous presentation of the disease between patients and across the varying disease evolution, and clearly illustrates the importance of appropriately stratifying estimates of costs of MG to allow for meaningful interpretation.

We identified one publication that reported estimates of costs associated with informal care of patients with MG. Schepelmann et al. [19] quantified annual costs associated with informal care by family and friends (based on the number of hours of informal care provided) in Germany at $1160, markedly lower than estimates from the same study for amyotrophic lateral sclerosis ($17,170) and facioscapulohumeral muscular dystrophy ($9230), as well as published estimates for German patients with Duchenne muscular dystrophy (DMD) ($20,266) [26]. Additionally, the indirect costs of MG, quantified as production losses due to patient absenteeism and presenteeism estimated using the human capital approach, were investigated by Schepelmann et al. [19] and Sonkar et al. [20]. Given that informal care accounts for the majority of the day-to-day long-term care of many chronic illnesses, in particular for chronic diseases with onset in childhood, further research of this cost category in MG is warranted. In particular, to avoid underestimating the monetary burden of the disease, future studies should aim to assess patient and caregiver indirect (productivity) costs and informal care costs as separate mutually exclusive subsets of total costs [6].

There are several implications of our review for health policy and future research. First, it is important to underscore that the outcomes do not provide any direct guidance of the cost-effectiveness of current or forthcoming health technologies targeting MG (as such economic evaluations compare both costs and benefits from alternative uses of resources). That being said, our results do show that, based on the existing body of evidence, it may prove challenging to conduct economic evaluations of treatments for MG considering the lack of comprehensive cost data in many settings. Indeed, for most evaluations and countries, depending on the complexity of the underlying cost-effectiveness model and the analysis, it will likely be necessary to conduct new cost studies. Second, considering the relatively high inter-patient variability in costs observed in our review, it appears essential to appropriately stratify costs (and related health economic outcomes) in future research, and also carefully document employed study criteria to ensure adequate interpretation of validity, both internal and external. Third, due to the relatively high costs associated with the treatment and management of the disease, it is not obvious that an intervention significantly improving prognosis for survival in MG would be cost-effective. This phenomenon, which was recently discussed in the context of DMD [27], emerges when the annual direct medical cost of illness is greater than the willingness to pay (WTP) for the effect outcome of interest [e.g. quality-adjusted life-years (QALYs), constructed by multiplying every life-year with a quality weight reflecting health-related quality of life] as applied in the evaluation. For example, using data from Guptill et al. [12], extending life by 1 year for a US patient with MG would, on average, be associated with a direct medical cost of $23,250 (not accounting for the cost of the intervention). This cost can then be related to the benefit, which is 1 life-year, or 0.69 QALY’s (using recently published SF-6D utility data for MG from Barnett et al. [28]), resulting in an incremental cost-effectiveness ratio (ICER) of $23,250/0.69 ≈ $35,000. Considering that prices for orphan drugs in many cases exceed $100,000 per annum [29], the total cost per QALY would be $135,000, higher than commonly employed WTP thresholds for QALYs in most jurisdictions. Accounting for additional disease-related costs, such as direct non-medical and indirect costs, this estimate would increase considerably.
Economic Costs of Myasthenia Gravis

That being said, future treatments may be associated with significant cost offsets (e.g. from avoiding hospitalizations), which would alter the distribution of costs and evaluation outcomes. Fourth, and last, from our review it is evident that any measures that help reduce the need for IVIG/PLEX (e.g. careful compliance to care guidelines, timely discontinuation of treatments for non-responders, and alternative/new therapies) would have a major impact on the individual cost burden of MG.

A limitation with our review is related to the fact that we, due to considerable inter-study heterogeneity, were unable to perform a proper meta-analysis [30]. Given that our search strategy limited the review to publications indexed in five principal bibliographic databases, studies published in local journals were not covered, which could potentially help explain the low number of studies for some geographical settings and regions. Concerning our findings, it is also worth noting that the costs identified in this review would not be expected to be directly transferable to other settings (because of, e.g., local/national prices and healthcare systems). Additionally, older point estimates (e.g. from Souayah et al. [21], Mandawat et al. [15], and Schepelmann et al. [19]) should be interpreted with some caution, as they may not be representative of the current medical management of the disease, and because opportunity costs of the underlying resources may have developed differently than inflation. Finally, despite being attributed a relatively low risk of bias as assessed using the NOS, all of the included studies were observational in nature, which means that they may still lack quality (due to, e.g., selection, confounding, and/or information bias). That being said, it should be noted that intervention-specific costs reported by Furlan et al. [10] were derived based on clinical data from a randomized controlled trial, which would imply a lower risk of confounding with respect to treatment allocation and associated outcomes.

5 Conclusion

We show that the current body of literature of costs of MG is sparse, limited to a few geographical settings and resource categories, mostly dated, and subject to non-trivial variability, both within and between countries. Our synthesis will help researchers and decision-makers identify gaps in the local health economic context of MG and inform future cost studies and economic evaluations in this patient population.

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Author Contributions Dr. Landfeldt conceptualized and designed the study, conducted the literature review and the analysis, led the interpretation of findings, drafted the manuscript, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Dr. Pogoryelova conducted the literature review, interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Professor Sejersen interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Professor Zethraeus interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Dr. Breiner interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted. Professor Lochmüller conceptualized and designed the study, interpreted the findings, critically reviewed the manuscript for important intellectual content, and approved the final manuscript version as submitted.

Data Availability Statement All data analysed as part of this study are included in this published article (and its supplementary information files).

Compliance with Ethical Standards

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Conflict of interest Dr. Landfeldt is an employee of ICON plc (Stockholm, Sweden), outside the submitted work. Dr. Pogoryelova is an employee of Absolute Antibody (Red Car, UK), outside the submitted work. Professor Sejersen, Professor Zethraeus, Dr. Breiner, and Professor Lochmüller declare no competing interests.

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