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REVIEW

A systematic review of myasthenia gravis complicated with myocarditis

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[Correction added on 30 August 2021, after first online publication: Peer review history statement has been added.]

Abstract

Among many of the autoimmune diseases observed in patients with myasthenia gravis (MG), myocarditis is one of the most critical. The goal of this review is to systematically describe and investigate the characteristics of MG complicated with myocarditis. We identified 183 records in PubMed (MEDLINE), Web of Science, and EMBASE from 1948 to September 10, 2020. Studies were included if they presented clinical data on MG complicated with myocarditis. Of the 35 patients from 28 studies in this review, 57.14% (20/35) were males, with a mean age of 59.11 ± 15.87. Dyspnea was the most common cardiac symptom accounting for over 60% in the study. Among the 35 patients, 13 cases of myocarditis occurred concomitantly with MG and the longest interval between MG and myocarditis was 7 years. Forty percent of patients developed myocarditis caused by immune checkpoint inhibitors (ICI). Among the patients with myocarditis, over half of the patients were diagnosed by myocardial biopsy. After active immune regulation and symptomatic treatment, only 15 of 35 patients with MG complicated with myocarditis improved, 18 patients died during hospitalization, one patient died due to tumor progression and 1patient died 5 years later. The prognosis of patients with MG complicated with myocarditis is poor, and myocardial enzymes and other indexes need to be monitored for patients taking ICI drugs. Patients with dyspnea who are still not ideally treated by mechanical ventilation should be vigilant against the occurrence of MG complicated with myocarditis.

KEYWORDS
immune checkpoint inhibitors, myasthenia gravis, myocarditis, review

1 | INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune disease that mainly involves acetylcholine receptors (AChR) on the postsynaptic membrane at the neuromuscular junction, and is mainly mediated by AChR antibodies, cellular immunity, and complement. The main clinical manifestation is local or systemic skeletal MG, which usually worsens after exercise and alleviates after rest or treatment with cholinesterase inhibitors (Conti-Fine et al., 2006; Kon et al., 2013).

Among the many autoimmune diseases observed in patients with MG, myositis and/or myocarditis are the most critical disorders, although the frequency of these in all patients with MG is generally

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low, ranging from 0.9% to 2.3%.(Santos et al., 2017; Suzuki et al., 2009). The study revealed that patients with MG having thymoma, female patients, and older patients were prone to developing myositis and/or myocarditis. They also found that myocarditis is a critical disease in patients with MG because the mortality due to myocarditis in the cohort of patients with MG was 42% (Kufukihara et al., 2019). MG is also the most commonly reported neuromuscular immune-related adverse effects (irAEs) associated with programmed cell death protein 1 (PD-1) inhibitors, with an incidence ranging from 0.12% to 0.2% (Konstantina et al., 2019; Suzuki et al., 2017). Immune checkpoint inhibitors (ICI) such as PD-1 are causative agents in the development of new onset MG. ICI-related MG is usually severe and often accompanied by myocarditis and myositis. The clinical features can be summarized as follows: (1) the onset occurred in the early phase after ICI treatment with rapid progression; (2) the disease was severe with higher frequencies of myasthenic crisis; (3) marked elevation of CK levels; and (4) immunosuppressive therapy was effective (Suzuki et al., 2017; Takai et al., 2020). Myocarditis can be a fatal immune-mediated adverse event in ICI-related MG (Suzuki et al., 2017). Since MG was generally severe in patients complicated with myocarditis, it is necessary to discriminate between an MG crisis and respiratory insufficiency due to myocarditis (Kufukihara et al., 2019).

MG involving myocardium is relatively rare. In recent decades, there have been a small number of case reports and reviews of immunosuppressant-related neuromuscular disease, but there has been no summary analysis of the MG phenotype of myocarditis. Therefore, the aim of this review is to systematically describe and investigate the characteristics of MG complicated with myocarditis.

2 | METHODS

2.1 | Data sources and study eligibility criteria

We identified 183 records in PubMed (MEDLINE), Web of Science, and EMBASE from 1948 to September 10, 2020. Studies were included if they presented clinical data on MG complicated with myocarditis. All types of study designs were included.

Articles that reported original data (age, sex, main symptoms, serological examination, cardiac examination, clinical outcome, etc.) in patients with MG and myocarditis were considered eligible. We included all types of study designs and even case reports. Articles without an (English) abstract, reviews, editorials, conference abstracts, and comments were excluded. Two members of the review team (WC and MY) independently assessed the titles and abstracts of all potentially relevant publications that were identified in the search. The decisions of the two reviewers about inclusion/exclusion were compared and, in cases of disagreement, were resolved by asking a third reviewer (TS) to achieve consensus. Subsequently, the same two reviewers evaluated the full text of all potentially eligible articles. Decisions about inclusion and exclusion were again compared and, in case of disagreement, resolved by asking the third reviewer in order to achieve consensus.

2.2 | Data analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows version 20.0). Descriptive analyses were performed to evaluate demographics and clinical features. Categorical variables are described as frequencies, while continuous variables were tested for normality and are presented as mean ± standard deviation (SD) or median ± interquartile range in cases of skewed data. The chi-square or Fisher's test was used for categorical variables, and Student's *t*-test was used for continuous variables. All statistical tests were two-sided at the significance level of .05.

3 | RESULTS

3.1 | Study selection and basic characteristics

We obtained 183 potentially relevant records identified from PubMed (MEDLINE), Web of Science, and EMBASE from 1948 to September 10, 2020, as demonstrated in Figure 1(a). According to Figure 1(b), ICI-related cases have been published since 2017. Studies were included if they presented clinical data on MG complicated with myocarditis. A total of 128 records were excluded for not concerning MG and myocarditis based on the title and abstract. In total, 55 articles were reviewed in detail. Reasons for exclusion are reported in Figure 2. Finally, 28 studies met the inclusion criteria and were included in the review. Among the 28 publications, there were 25 case reports, two letters and one article. A total of 35 patients were included in 28 studies, including 14 ICI-related and 21 non-ICI-related patients (Figure 1(b)). The clinical data of all patients are shown in Table 1.

Of the 35 patients in this review, 57.14% (20/35) were males, with a mean age of 59.11±15.87 (M ± SD). No significant difference was found in the comparative analysis of the mean age between females and males (59.75±17.30 vs. 58.27±14.29, $p = .789$).

3.2 | Clinical characteristics of MG complicated with myocarditis

As shown in Table 1, among the 35 patients, 13 cases of myocarditis occurred concomitantly with MG and the longest interval between MG and myocarditis was seven years. Of the 13 cases, 8 cases did not provide a specific time from clinical presentation to diagnosis. Among the four patients who had presented earlier, three patients were diagnosed as MG and myocarditis 5 days after the onset of symptoms, and one patient was diagnosed 1 day later. One patient with MG symptoms and dyspnea or other cardiac symptoms was diagnosed with MG and myocarditis 2 years later. Heart disease related symptoms were unknown in 3 of the 28 records included in the analysis. Among the 32 patients with complete clinical symptom data, dyspnea was the most common symptom of heart disease, accounting for over 60%.

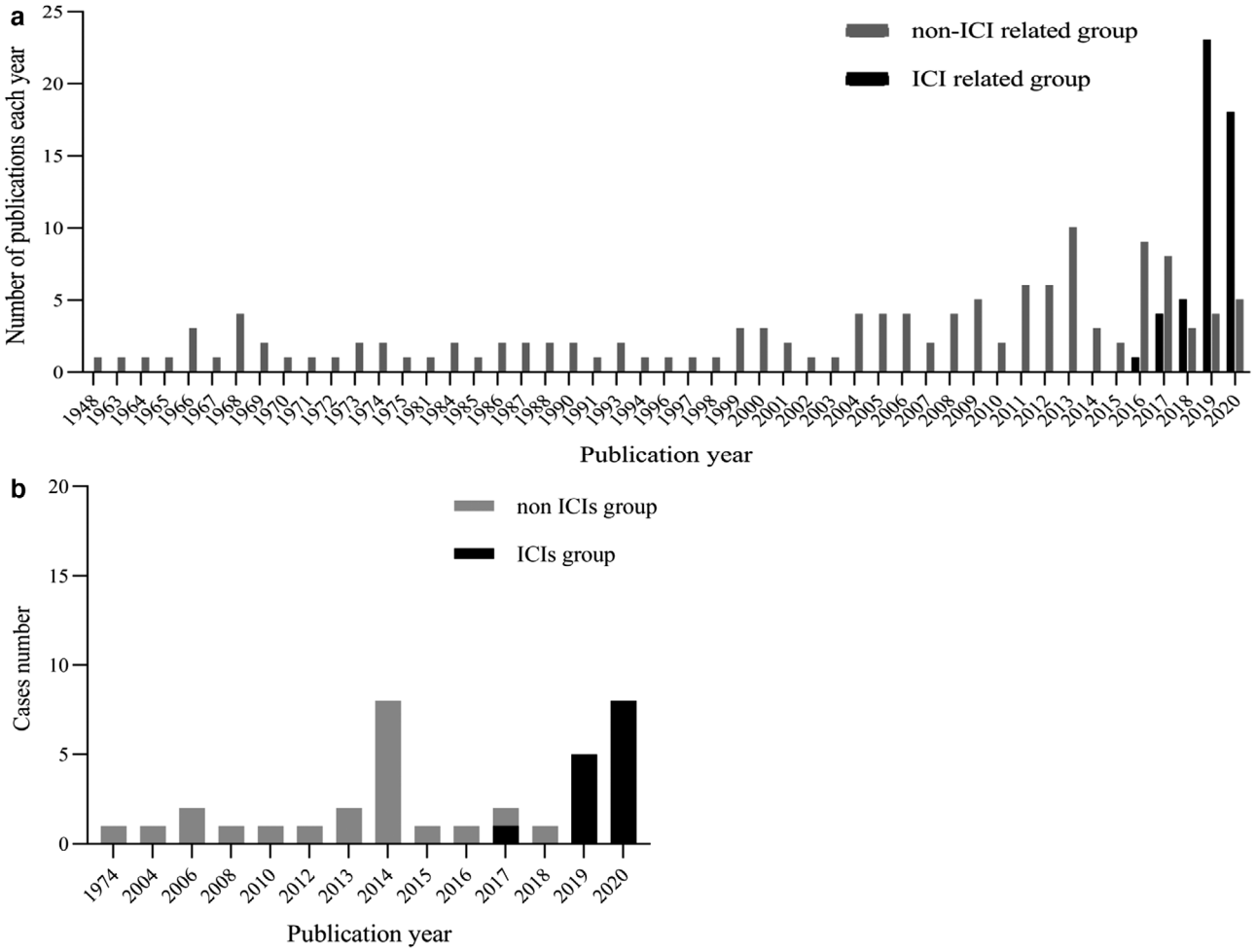

FIGURE 1 The number of publications and enrolled patients on "myasthenia gravis" and "myocarditis" from 1948 to 2020. (a) The number of publications and (b) the number of ICI-related and non-ICI-related patients with MG with myocarditis in different years

Of the 35 patients with MG, 14 (14/35 = 40%) of them developed myocarditis caused by ICI, such as bevacizumab, pembrolizumab, nivolumab, ipilimumab, etc. Among the 35 patients with myocarditis, 13 patients were diagnosed by clinical symptoms and auxiliary examination (no cardiac magnetic resonance imaging and myocardial biopsy), 4 patients were diagnosed by clinical symptoms and cardiac magnetic resonance imaging, and the remaining 18 patients were diagnosed by myocardial biopsy.

The main treatments for myocarditis in the records included stopping antitumor immunotherapy, methylprednisolone, intravenous immunoglobulin (IVIG), rituximab, plasma exchange therapy, inserting a pacemaker, implantation of a cardiac defibrillator, electrical cardioversion, mechanical ventilation, intra-aortic balloon pump, extracorporeal membrane oxygenation (ECMO), etc. After active immune regulation and symptomatic treatment, only 15 of 35 patients with MG complicated with myocarditis have improved, 18 patients died during the hospitalization, 1 patient died because of tumor progression, and 1 patient died 5 years later (Table 1).

As shown in Table 2, the ratio of thymoma in the ICI-related group was significantly lower than that in non-ICI-related group (35.71% vs. 64.29%, $p = .004$). But between these two groups, we found no differences in age, sex, proportion of simultaneous diagnosis of MG and myocarditis, and the proportion of deaths. Among patients without thymoma, ICI-related patients were older than non-ICI-related patients (71.33 ± 11.61 vs. 48.00 ± 20.66, $p = .030$). However, in these two groups of patients, combined with thymoma, we found no differences in age, sex, the proportion of MG and myocarditis diagnosed at the same time, as well as the proportion of deaths in patients.

4 | DISCUSSION

This is the first systematic review of MG complicated with myocarditis. In a comprehensive analysis of 35 patients with MG complicated with myocarditis in 28 studies, the death group accounted for a high proportion (57.1%). Therefore, we need to further summarize and understand the characteristics of MG complicated with myocarditis.

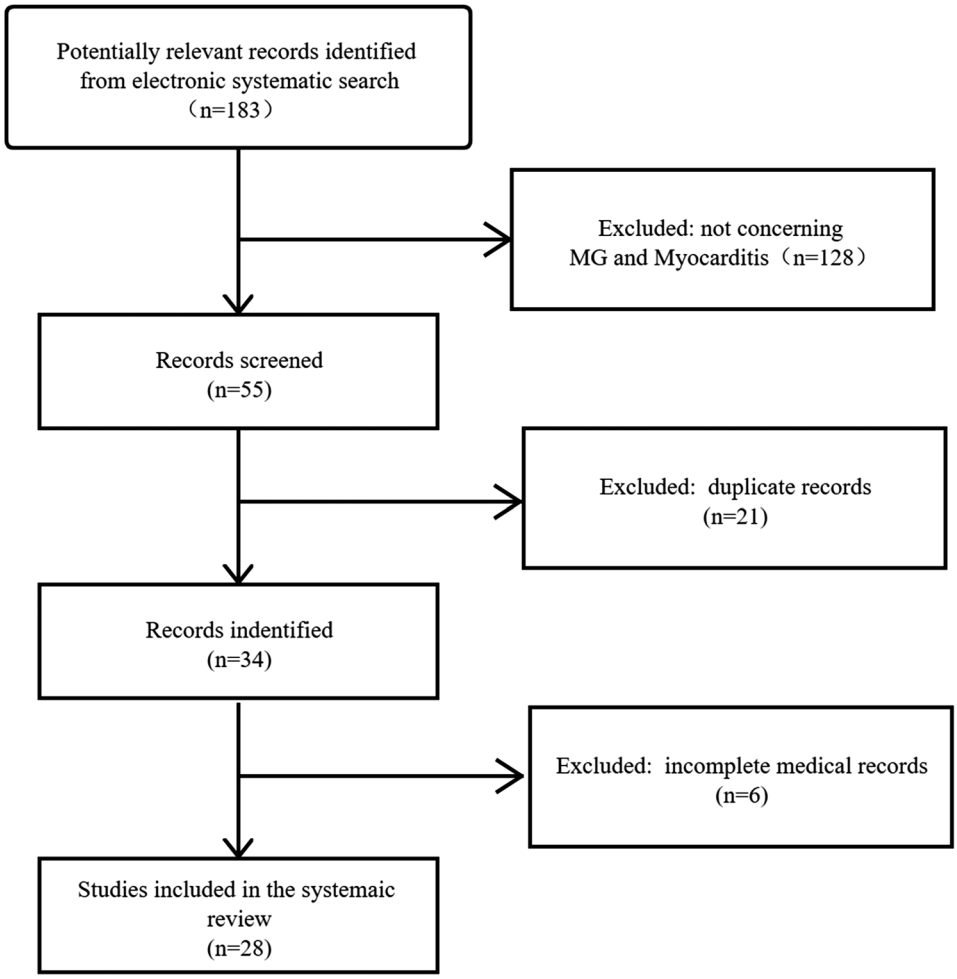

FIGURE 2 Flow diagram of the inclusion of studies

4.1 | The epidemiology of MG

MG is an autoimmune disease characterized by muscle weakness caused by neuromuscular transmission disorders caused by autoantibodies binding to the postsynaptic membrane of the neuromuscular junction. The disease is mainly mediated by acetylcholine receptor, and studies have also found that a variety of autoantibodies are involved in the pathogenesis of MG. The annual incidence of MG is 8.0–20.0/1000,000, which can occur in all age groups (Deenen et al., 2015). Before the age of 40, the incidence rate is higher in females than in males; the incidence in females is similar to that in males between 40 and 50 years; after 50 years, the incidence in males is slightly higher than that in females (Conti-Fine et al., 2006; Deenen et al., 2015). However, the age at onset of the patients with MG and myocarditis (mainly the late onset age range of >50) is higher than that of the usual population of all patients with MG. This may be related to the fact that people of the above age groups are more likely to have heart disease or risk factors for heart disease (Limaye et al., 2016). The clinical manifestation of the disease is complex, and the diagnosis and treatment are still facing great challenges.

4.2 | The characteristics of MG complicated with myocarditis

MG can involve multiple organ systems, but cardiac involvement is rarely reported. Bramwell (1901) described a 30-year-old male patient with MG with tachycardia and heart failure in 1901. He first proposed that MG may cause cardiomyasthenia, and put forward the concept of Herzmyasthenie. Gibson (1975) found that there were 126 patients with abnormal ECG in 245 patients with MG; the incidence rate was over 51.4%, but most of the subjects were elderly patients, and some were complicated with coronary heart disease or had risk factors for coronary heart disease, which may lead to deviation in the results. Suzuki et al. (2014) found that 42 of 650 patients with MG had ECG and myocardial enzyme changes. After removing influencing factors such as cardiovascular disease, malignant tumor invasion and thymic radiotherapy, and chemotherapy injury, eight patients were diagnosed with myocarditis and most were complicated with thymoma. Among the 28 papers included in this study, the average age of onset of 35 patients was 59.1, and 23 cases (65.7%) were complicated with thymoma.

TABLE 1 Detailed description of the characteristics of myasthenia gravis complicated with myocarditis

Study/year	*N*	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Fuentes-Antrás et al. (2020)	1	75	M	Bilateral ptosis, oculomotor palsy, proximal muscular weakness, dysphonia, and dysphagia; AChR-Ab(+); antistriated muscle antibodies(+)	Metastatic lung adenocarcinoma (chemotherapy and bevacizumab), thyroiditis, hepatitis, myositis	24 h	Dyspnea	ECG revealed a complete atrioventricular block.	Postmortem examinations revealed necrotizing myocarditis	NIMV; pyridostigmine and Methyl-prednisolone, Infliximab and IVIGs	Death occurring at Day 7 of hospitalization
Hyun et al. (2020)	1	45	F	Quadriparesis, ptosis, and dyspnea on exertion; AChR-Ab(+)	Refractory thymoma after administration of pembrolizumab, chronic hepatitis B carrier, hepatic dysfunction	9 years	Progressive dyspnea on exertion and orthopnea	CK 7552 U/L (UNL, 135 U/L), CK-MB, 547 ng/mL (UNL, 6.3 ng/mL), Tn I 42 ng/mL (UNL, 0.04 ng/mL), AST 877 IU/L, ALT 610 IU/L; dynamic ECG changes, including complete atrioventricular block, right and left bundle branch blocks, asystole, and ventricular tachycardia; TTE(−)	NA	ECMO, high-dose intravenous steroid therapy; cardiorenal syndrome developed and necessitated continuous renal replacement therapy	Passed away on Day 10 of admission
Jeyakumar et al. (2020)	1	86	M	Decreased vision in the left eye, double vision, difficulty swallowing or walking, muscle aches, or tenderness; antistriated muscle antibody(+), AChR-Ab(+)	Metastatic cutaneous squamous cell carcinoma (cemiplimab therapy), sick sinus syndrome status after pacemaker placement, hypertension, and chronic kidney disease	0 days	Shortness of breath, chest pain	CK 6407 IU/L, TnT 1557 ng/L; AST 532 IU/L, ALT 214 IU/L; ECG: inferior wall ischemia and showed a new right bundle-branch block; TTE(−)	Left and right heart catheterization with endomyocardial biopsy was performed and revealed an active necrotizing lymphocytic myocarditis	ICU, SIMV, 1 g intravenous methylprednisolone, plasma exchange therapy for 5 days, IVIG, continuous renal replacement therapy	Death (hyperkalemia and severe metabolic acidosis)

(Continues)

TABLE 1 (Continued)

Study/year	N	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Leaver et al. (2020)	1	55	M	Blurred vision, mild bilateral ptosis, and fatigable left arm abduction; EMG(+)	Cerebral and pulmonary melanoma metastases (dual ICI therapy with nivolumab and ipilimumab), hypertension	0 days	NA	CK 613 U/L, TnI 240 ng/L (<26), ECG demonstrated nondynamic deep anterolateral T-wave inversion; TTE(−), cardiac MRI demonstrated a small focal area of subendocardial late gadolinium enhancement in the basal inferolateral wall	NA	Stop ICI therapy; prednisone, IVIG, MMF plasma exchange	Improved (disease remission)
Szuchan et al.(2020)	1	70	F	Weakness (muscle-specific tyrosine kinase (MuSK) and acetylcholine receptor (AChR-Ab) (+))	Recurrent/metastatic thymic carcinoma (bone and pleural metastases)	0 days	Dyspnea, orthopnea	TnT 10.50 ng/L, CK 1667 U/L, CK-MB 107 U/L, ECG was suspicious for myocardial infarction, coronary angiogram(−)	EMB: mild myocyte hypertrophy with diameters in the 30–40 mm range; lipofuscin granules were observed in the perinuclear region of myocytes	Placed dual-chamber pacemaker; pulse-dose methylpred-nisolone (NIPAP); pyridostigmine; plasmapheresis	Discharged home in stable condition
Takai et al. (2020)	1	77	M	Right ptosis and diplopia; AChR-Ab(+) and antimuscle-specific kinase (MuSK)) (−)	Metastatic bladder cancer (pembrolizumab)	4 days	Dyspnea	CK 8574 U/L, CK-MB 207 U/L, TnT 9.28 ng/ml, NT- pro BNP 6854 pg/ml; ECG showed ST elevation and left bundle branch block with a wide QRS, and TTE: diffuse loss in wall motion and 29% with ejection fraction	NA	IVIG, prednisone, along with dobutamine, carperitide, and furosemide.	A sudden drop in blood pressure and died 4 days after admission

(Continues)

TABLE 1 (Continued)

Study/year	*N*	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Vermeulen et al. (2020)	1	53	F	Limb-girdle weakness, dropped head, dyspnoe, dysphagia, ptosis, and fatigable horizontal diplopia; EMG(+)	Melanoma (BRAF wild type), stage IV (ipilimumab), resection of inguinal lymph nodes (2015)	0 days	Dyspnea	Deficiency	Biopsy m. deltoideus (right): multifocal necrotic fibers; multifocal endomysial and perivascular immune infiltrate	Plasma exchange (five sessions on alternate day)	Died several months later due to progressive oncological disease
Xing et al. (2020)	1	66	M	Dysphagia, hypercapnic respiratory failure, ptosis, ophthalmoplegia	Thymoma (radical resection of thymoma and left lung adenocarcinoma), right lung adenocarcinoma underwent video-assisted thoracoscopy pulmonary wedge resection	8 days	Shortness of breath	CK 11,919 U/L, MB 3000 ng/ml, TnT 0.916 ng/ml, ECG: complete right bundle branch block complicated with complete atrioventricular block; TTE(−)	NA	Methylprednisol and IVIG; plasma exchange, pyridostigmine bromide; insert temporary pacemaker, NIPPV; tracheotomy	Improved
Fazel and Jedlowski (2019)	1	78	F	Upward and downward gaze palsies, along with unsteady gait; weakness and myalgias of proximal muscles bilaterally; antistriational antibodies(+)	Hypertension, intermittent asthma, prior pulmonary embolism, depression, and metastatic melanoma (after wide local excision)	0 days	Dyspnea	AST 683 IU/L, ALT 315 IU/L, CK 9198 IU/L, TnT 8.57 ng/ml; TTE(−); myositis antibody(−), lower limb MR considered myositis	NA	Ipilimumab-nivolumab therapy, methylpred-nisolone, IVIG (2 g/kg IV daily for 2 days); plasmapheresis	Death (the drug effect is poor)
Konstantina et al. (2019)	1	30	F	Unilateral eyelid drop, diplopia; AChR-Ab(+)	De novo metastatic B3 thymoma	2 days	Acute chest pain, dyspnea	ECG: II, III, aVR, and rising levels; CK and Tn I↑;acute increase in her liver transaminases	NA	Pembrolizumab, pyridostigmine, prednisolone 2 mg/kg, IVIG (400 mg/kg for 5 days), rituximab	Death (septic shock)

(Continues)

TABLE 1 (Continued)

Study/year	*N*	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Shirai et al. (2019)	1	83	M	Bilateral ptosis, diplopia, weakness of neck flexor and extensor, and bilateral thigh myalgia, dysphagia; AChR-Ab(+), Str-Abs(+), anti-titin antibody(+); anti-Kv1.4 antibody(+);	Melanoma; ICI-related hepatitis; myositis	1 day	Dyspnea	AST 328 U/l, ALT 337 U/l; CK 5567 U/ l, CK-MB 177 ng/ml, TnT 0.337 ng/ml, BNP 42.1 pg/ml; ECG: T-wave abnormality, wide QRS, and first-degree atrioventricular block; TTE(−)	NA	Four cycles of plasma exchange therapy were carried out simultaneously with steroid pulse therapy	Improved
So et al. (2019)	1	55	F	Progressive ophthalmoplegia, ptosis, dysphagia, dyspnea, and limb weakness; AChR-Ab(+)	Metastatic melanoma, thymectomy for thymoma; myositis	6 years	Dyspnea	CK (max 13652 IU/L), CK-MB↑, TnT and TnI↑; ECG: QRS complex tachycardia; TTE: dyssynchrony of the left ventricle and reduced EF (45%)	NA	NIMV; IVIG, 0.4 g/kg/day, 5 days; immunotherapies (four cycles of IVIG and steroid pulse plus two cycles of plasma exchange);	Symptoms improved gradually
Valenti et al. (2020)	1	66	M	Binocular diplopia, fatigue, mild dyspnea, and upper back pain, limited abduction of both eyes, mild left ptosis; AChR-Ab(−); EMG(+)	Nonmicrocytic lung carcinoma with hepatic and bone metastases (first line, Nivolumab (anti-PD-1) + ipilimumab (anti-CTLA-4))	0 day	Dyspnea and upper back pain	CK 2148 U/L, TnT 1051 ng/ml; ECG, TTE and cardiac MRI (muscle inflammation on MRI) revealed a new-onset atrial fibrillation and mild left ventricle dysfunction	NA	Stop antitumor immunotherapy; intravenous high-dose steroid treatment (prednisolone 2 mg/kg/day)	Two months later the patient was deceased because of tumor progression
Priemer et al. (2018)	1	61	M	Myasthenia crisis; AChR-Ab(+)	Metastatic thymoma (after thymectomy and left upper pneumonectomy, on chemotherapy (napabucasin and paclitaxel, 1 cycle))	0 day	Arrhythmia; cardiogenic shock	Myocardial enzyme↑; ECG: sinus tachycardia with premature ventricular complexes in a pattern of bigeminy	Lymphohistiocytic infiltrates with multinucleated giant cells in the myocardium and skeletal muscles, including the diaphragm	Edrophonium, plasma exchange, intravenous methylprednisone	Death

(Continues)

TABLE 1 (Continued)

Study/year	*N*	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Fukasawa et al.(2017)	1	69	F	Diplopia and adduction disorder of left eye; AChR-Ab(+)	Lung cancer (nivolumab, third cycle)	0 day	Arrhythmia; cardiogenic shock	CK 1156 IU/L, CK-MB and TnI↑;ECG:diffuse elevated ST, atrioventricular block, multiple ventricular premature beats	Myocardial inflammation and myocardial necrosis, interstitial edema. $CD8^+$ T, $CD4^+$ T infiltration, cardiomyocyte HLA antigen(+) , virus(−)	Pacemaker, noninvasive ventilation, methylprednisolone	Rapid improvement
Shintaku et al. (2017)	1	54	F	Muscle weakness of the extremities and ptosis of the eyelid	NA	2 years	NA	ECG: Ventricular tachycardia;CK 6024 IU/L, CK-MB121 IU/L, MB 1720 IU/L; TTE: weakness of left ventricular motion, EF10%、CI↓;coronary angiography (−)	Chronic myocarditis, focal giant cell infiltration. Focal coagulative necrosis and degeneration of myocardium. HLA-DR antigen (−) , bacteria virus (−)	Prednisone 20 mg/day, implantation of cardiac defibrillator	Death (heart failure)
Limaye et al. (2016)	1	65	M	Muscle weakness, shortness of breath, dysphagia; AChR-Ab(+); EMG(+)	NA	NA	Chest pain	ECG:Increased ST in multiple leads, ventricular tachycardia and cardiac arrest;TnIn;coronary angiography (−) ;TTE: EF 30%;MRI: myocardial diffuse delayed enhancement	NA	Electrical cardioversion, endotracheal intubation; prednisone 60 mg/day, MMF	Improved (heart failure improved after 2 years, EF 40%)

(Continues)

TABLE 1 (Continued)

Study/year	*N*	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Shah et al. (2015)	1	70	M	Fatigue, dysphagia, proximal muscle weakness, antiskeletal muscle antibody, and anti-ACH+	Thymoma, nodule of left forearm	NA	Dyspnea	CK 3956 IU/L, TnT 1376 ng/ml; ECG: supraventricular tachycardia with abnormal R wave;TTE (−)	NA	Methylprednisolone 1 g/day × 3 days, followed 40 mg/day; IVIG	Improved
Saito et al. (2013)	1	31	M	NA	Invasive thymoma (B2, IVa) (after chemotherapy); polymyositis	3 years	Cardiogenic shock	CK 6300 U/L, CK-MB 233 U/L; ECG: ventricular tachycardia; TTE: EF 20%;coronary angiography (−)	Cardiac biopsy revealed lymphocytic myocarditis	IABP and ECMO, methylpred-nisolone 1 g/day × 3 days, followed 1 mg/kg/day	Improved (with a recovery of EF to 74%
Suzuki et al. (2014)	8	62	M	Dysarthria, diplopia, ptosis, myasthenia crisis; AChR-Ab(+)	Invasive thymoma (B1, IVa); myositis	211 months	Shortness of breath, tachycardia, shock	ECG: ventricular tachycardia;CK 9835 U/L	Giant cell myocarditis	High-dose methylpred-nisolone, tacrolimus, plasma exchange, IVIG, catecholamine	Death
		69	F	Cervical myasthenia, myasthenia crisis; AChR-Ab(+)	Mediastinal mass, myositis	0 day	Shortness of breath, chest pain, heart failure	ECG: repetitive ventricular tachycardia and apical torsional ventricular tachycardia; CK 1250 U/L	NA	High-dose methylpred-nisolone, catecholamine	Death
		45	M	Ptosis, dysphagia, myasthenia crisis;AChR-Ab(+)	Thymoma (AB, II)	0 days	Shortness of breath	ECG: complete atrioventricular block; CK 135 U/L	NA	High-dose methylpred-nisolone, tacrolimus, plasmapheresis, IVIG	Death
		44	F	Ptosis, diplopia, myasthenia of extremities; AChR-Ab(+)	Thymoma (B1, III)	82 months	Cardiac arrest	ECG: QT interval prolongation; CK 467 U/L	NA	High-dose methylpred-nisolone	Death

(Continues)

TABLE 1 (Continued)

Study/year	N	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
		53	F	Ptosis, myasthenia, dysarthria, myasthenia crisis;AChR-Ab(+)	Thymoma (B1, III), dilated cardiomyopathy	118 months	Shortness of breath and shock	ECG:Tachycardia and T-wave abnormality; CK 397 U/L; coronary angiography (–)	NA	IABP; high-dose methylpred-nisolone, tacrolimus	Drug control
		45	F	Diplopia, myasthenia, dysarthria, myasthenia crisis;AChR-Ab(+)	Thymoma (B3, II)	13 months	Chest pain	ECG: Tachycardia and T-wave abnormality; CK 157 U/L; TTE: weakness of left ventricular motion;coronary angiography (–)	NA	High-dose methylpred-nisolone, plasmapheresis	Improved (almost asymptomatic)
		51	M	Cervical, masticatory, limb muscle weakness, dysarthria;AChR-Ab(+)	Thymoma (B2, II)	0 days	Shortness of breath	ECG: sinus arrest and paroxysmal atrial flutter; CK 66 U/L	NA	Pacemaker; prednisone, plasma exchange	Drug control
		80	F	Neck muscle, limb myasthenia, dysarthria, myasthenia crisis;AChR-Ab(+)	Thymoma (AB, III), myositis	0 days	Shortness of breath, chest pain, lower limb edema	ECG: atrioventricular block and atrial tachycardia;CK 3107 U/L; MRI: myocardial imaging delay; coronary angiography (–)	NA	Pacemaker; high-dose methylpred-nisolone, IVIG	Improved (almost asymptomatic)
Kon et al. (2013)	1	80	M	Fatigue, ptosis, diplopia;EMG(+), AChR-Ab(+), take hormones and anticholinergic drugs	Thymoma (B1)	16 years	Acute respiratory failure	EEG: poor increasing R wave and abnormal T wave; CK 5141 U/L, CK-MB 631 U/L, TnT 0.291 U/L	Myocardium: patchy myocardial fibrosis, infiltration of $CD8^+$ T cells and multinucleated giant cells	Endotracheal intubation, plasma exchange	Death

(Continues)

TABLE 1 (Continued)

Study/year	*N*	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Sasaki et al. (2012)	1	58	M	Myalgia, myasthenia; AChR-Ab(+)	Thymoma (B2, IVa) left pleural metastasis (carboplatin + paclitaxel)	3 days	NA	CK 7271 U/L, ALT 469 IU/L, AST 561 IU/L	Myocardium; inflammation containing multinucleated giant cells; no coronary artery abnormalities	NA	Death
Fayssoil et al. (2010)	1	25	M	Daily treatment of pistigmine, azathioprine, and prednisone	NA	0 days	Heart failure	ECG: sick sinus syndrome, TTE: EF 18%	Myocardium: nonspecific lymphocyte infiltration	Endotracheal intubation, ECMO (no immunosup-pressant in the first 7 days)	Improved (7 days later EF 50%)
HooKim et al. (2008)	1	72	F	Myasthenia	Azathioprine therapy after thymoma resection; hyperc-holesterolemia	7 years	Chest pain, shortness of breath and cardiac arrest after exercise	TNT 4.38 ng/ml, CKMB 711 U/L; ECG: increased ST in inferior leads; TTE: EF 40%;coronary angiography (–)	Myocardium: multinucleated giant cells and other inflammatory cell infiltration, myocardial fibrosis; virus (–)	NA	Death
van Haelst et al. (2006)	1	34	M	Shortness of breath and sweating	Thymoma after resection	NA	Heart failure	ECG:pathological Qs in leads V1–3 and II, III, and aVF; sustained polymorphic ventricular arrhythmias; TTE:echocardiography revealed a small heart with diffusely thickened walls of both ventricles; coronary angiography (–)	Myocardium:a dense inflammatory interstitial infiltrate that contains lymphocytes, epitheloid histiocytes, and Langhans giant cells	Methylprednisol 1 g/day × 3 days, cyclosporine and azathioprine and plasma-pheresis; ICD	Improved (6 months later EF 45% and EMB showed no GCM)

(Continues)

TABLE 1 (Continued)

Study/year	*N*	Age	Sex	Clinical features (MG)	Comorbidities	Interval between MG and myocarditis	Myocarditis		Pathology	Treatments	Outcome
							Clinical feature	Associated examination			
Joudinaud et al. (2006)	1	43	M	Shortness of breath	Thymoma after resection	NA	Cardiogenic shock	ECG:Diffuse low voltage and atrial fibrillation; TTE:biventricular diffuse hypokinesia, coronary angiography and PTCA (−)	Myocardium: diffuse myocardial necrosis and infiltration of multinucleated giant cells	Endotracheal intubation, ECMO	Death (MODS)
Tanahashi et al. (2004)	1	62	M	Muscle weakness was treated with prednisone and tacrolimus successively; AChR-Ab(+)	Invasive thymoma after postoperative radiotherapy; myositis	17 years	Weakness, shortness of breath	CK 563 IU/L; ECG:nonspecific ST changes and complete atrioventricular block	Infiltration of inflammatory cells such as multinucleated giant cells and diffuse myocardial degeneration can be seen in myocardium	Endotracheal intubation, methylprednisolone	Death
Namba et al. (1974)	1	57	F	Limb weakness;AChR-Ab(+)	Postoperative thymoma; myositis	5 years	Heart failure	ECG:ST-T change	Myocardium: multinucleated giant cell inflammation	Anticholinergic drugs and prednisone	Died 5 years later

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BNP, brain natriuretic peptide; CK, creatine kinase; CK-MB, CK-myocardial band; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ECG, electrocardiography; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; EMB, endomyocardial biopsy; EMG, electromyography; GCM, giant cell myocarditis; IABP, intra-aortic balloon pump; ICD, implantation of a cardiac defibrillator; irAEs, immune-related adverse events; IVIG, intravenous immunoglobulin; MB, myoglobin; MG, myasthenia gravis; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; NIMV, noninvasive mechanical ventilation; NIPPV, noninvasive positive pressure ventilation; PD-1, programmed cell death protein 1; TnT, troponin-T; TTE, transthoracic echocardiogram; UNL, upper normal limit.

TABLE 2 Clinical characteristics of the ICIs-related and non-ICIs-related patients with MG complicated with myocarditis

Clinical characteristics	Total ($n = 35$)	ICIs-related patients ($n = 14$)	Non-ICIs-related patients ($n = 21$)	*p*-Value	Patients with thymoma ($n = 23$)			Patients without thymoma ($n = 12$)		
					ICIs-related patients ($n = 5$)	Non-ICIs-related patients ($n = 18$)	*p*-Value	ICIs-related patients ($n = 9$)	Non-ICIs-related patients ($n = 3$)	*p*-Value
Sex, *n* (%)				.511			.155			1.000
Female	15(42.86%)	7(50.00%)	8(38.10%)		4(80.00%)	7(38.89%)		3(33.33%)	1(33.33%)	
Male	20(57.14%)	7(50.00%)	13(61.90%)		1(20.00%)	11(61.11%)		6(66.67%)	2(66.67%)	
Age, mean ± SD	59.11 ± 15.87	64.86 ± 15.66	55.29 ± 15.18	.080	53.20 ± 16.24	56.50 ± 14.49	.664	71.33 ± 11.61	48.00 ± 20.66	**.030***
State of myocarditis and MG, *n* (%)				.353			1.000			.523
Simultaneously	13(37.14%)	7(50.00%)	6(28.57%)		1(20.00%)	5(27.78%)		6(66.67%)	1(33.33%)	
Nonsimultaneous	22(62.86%)	7(50.00%)	15(71.43%)		4(80.00%)	13(72.22%)		3(33.33%)	2(66.67%)	
Prognosis, *n* (%)				1.000			.618			.523
Death	20(57.14%)	8(57.14%)	12(57.14%)		2(40.00%)	11(61.11%)		6(66.67%)	1(33.33%)	
Improved	15(42.86%)	6(42.86%)	9(42.86%)		3(60.00%)	7(38.89%)		3(33.33%)	2(66.67%)	
Combined with thymoma, *n* (%)				**.004***			–			–
Yes	23(65.71%)	5(35.71%)	18(85.71%)		–	–		–	–	
No	12(34.29%)	9(64.29%)	3(14.29%)		–	–		–	–	

Abbreviations: ICIs, immune checkpoint inhibitors; MG, myasthenia gravis; SD, standard deviation.

Myocarditis is the most important manifestation of MG involving the heart, and its pathogenesis is complex. A previous study suggests that giant cell polymyositis and myocarditis in patients with thymoma and MG is a postviral autoimmune process (Priemer et al., 2018). Romi et al. (2005) found that 48% of patients with MG had antirhabdomyosus antibodies (including myonectin antibody titin-Ab, ryanodine receptor antibody RyR-Ab, antivoltage-gated potassium channel antibody (Kv1.4-Ab)), and the positive rate of antibodies in patients with thymoma was over 97%. The study showed that anti-titin and anti-Kv1.4, but not antiryanodine receptor antibodies, were preferentially detected in patients with MG with myocarditis, and those with late-onset and thymoma-associated MG. Serial changes in the antibody index showed that anti-titin antibodies were present before the onset of myocarditis. In contrast, it is likely that the appearance of anti-Kv1.4 antibodies was correlated with the development of myocarditis. Recently, the clinical significance of antistriational antibodies has been reconsidered. Antistriational antibodies are detectable in the serum of these patients and are expected to be serological markers for serious irAEs (Kufukihara et al., 2019; Shirai et al., 2019). Among the 35 patients with MG complicated with myocarditis included in this review, the antibody positive rate was 68.6% (24/35). Of the 11 AChR antibody negative patients, six cases have been diagnosed with MG in the past (Fayssoil et al., 2010; HooKim et al., 2008; Joudinaud et al., 2006; Saito et al., 2013; van Haelst et al., 2006; Xing et al., 2020), three cases were positive for electromyography (Leaver et al., 2020 ; Valenti-Azcarate et al., 2020; Vermeulen et al., 2020), one case was positive for antistriational antibodies and complicated with myositis (Fazel & Jedlowski, 2019), and one case had typical clinical manifestations of MG and a corresponding clinical treatment was effective (Shintaku et al., 2017). Previous studies showed that myocarditis occurs in about 37.5% of patients with MG with positive antistriated muscle antibodies, and its mechanism may be related to the immune injury mediated by the binding of antibodies to specific antigens under the myocardial cell membrane (Espinosa & Kaplan, 1971). At the same time, it was found that HLA (Human Leukocyte Antigen) immune related genes and cellular immunity may also be involved in the pathogenesis of myocarditis (Fukasawa et al., 2017; Joudinaud et al., 2006; Kon et al., 2013; Shintaku et al., 2017).

The ICI stimulate a robust immune response leading to a potent antineoplastic effect and several irAEs including myocarditis, MG, myositis, hepatotoxicity, etc. (Deenen et al., 2015; Hyun et al., 2020; Szuchan et al., 2020). ICI are a class of medications that include PD-1 inhibitors (nivolumab) and cytotoxic T-lymphocyte associated protein 4 inhibitors (ipilimumab), which disinhibit the immune system and antitumor immune response by blocking immune checkpoint cytokines (Fazel & Jedlowski, 2019; Jeyakumar et al., 2020; Konstantina et al., 2019; So et al., 2019). ICI-related MG is usually severe and is frequently accompanied by myocarditis (Takai et al., 2020). In the review, we found that 40% of patients developed myocarditis caused by ICI. It is essential that patients with ICI-induced MG should be screened and monitored for myocarditis, a potentially fatal complication (Leaver et al., 2020; Vermeulen et al., 2020). The management of an irAE associated with ICI is based on corticosteroids and other immunomodulating therapies. Early recognition and prompt treatment are crucial for improving clinical outcomes (Valenti-Azcarate et al., 2020).

MG complicated with myocarditis has a variety of clinical manifestations, such as asymptomatic electrocardiogram, myocardial enzyme changes, fatigue, shortness of breath and decreased exercise tolerance, as well as heart failure and sudden death (HooKim et al., 2008). Due to the lack of specific symptoms or signs, myocarditis is easily misdiagnosed as skeletal MG, thus delaying the diagnosis and eventually leading to a poor prognosis. Individuals with MG usually develop malignant arrhythmias and life-threatening heart failure 13–211 months after the diagnosis of MG. Some patients can also be treated at the first manifestation of fulminant myocarditis (Suzuki et al., 2014). The electrocardiographic changes in patients with MG having myocarditis were mostly nonspecific ST-T changes, including sinus bradycardia, sinus tachycardia, atrial extrasystole, ventricular extrasystole, incomplete bundle branch block, and even ventricular tachycardia, torsade de pointes and complete atrioventricular block. Although the electrocardiogram examination has no specific indication, it can be used for the early screening of MG myocarditis because it is simple and noninvasive. Myocarditis often has no change in myocardial morphology, echocardiography shows that the heart shape is normal, while the ejection fraction and cardiac index can be significantly decreased. Except for a few patients with stress cardiomyopathy with spherical heart changes during crisis, angiocardiography usually found no abnormality (Romi et al., 2005). In recent years, some scholars have proposed that cardiac magnetic resonance imaging plays an important role in the diagnosis of myocarditis (Limaye et al., 2016). In our study, 51.4% (18 /35) of patients with MG complicated with myocarditis were diagnosed by myocardial pathological biopsy. Myocardial biopsy is still the gold standard for the diagnosis of myocarditis as electrocardiogram and echocardiogram may not reveal dysfunction (Jeyakumar et al., 2020; Szuchan et al., 2020). Most of the above pathology showed the infiltration of chronic inflammatory cells such as multinucleated giant cells and lymphocytes, myocardial degeneration, necrosis, and fibrosis. Immunohistochemistry showed that cardiomyocytes expressed HLA, CD68, CD3, and other antigens without any bacterial or viral infection. Biopsy was often accompanied by giant cell inflammation of the skeletal muscle (Joudinaud et al., 2006; Kon et al., 2013; Namba et al., 1974; Saito et al., 2013; Sasaki et al., 2012; Tanahashi et al., 2004).

Brompistigmine can be used as a single drug for long-term treatment in patients with mild MG, but it should usually be given in combination with immunosuppressants. Glucocorticoid is the first choice of immunotherapy in patients with MG complicated with myocarditis (Xing et al., 2020). Nonsteroid drugs such as azathioprine, cyclosporine A, mycophenolate mofetil, methotrexate, and tacrolimus can be considered when the curative effect of sufficient glucocorticoid is not ideal, obvious adverse reactions or symptom recurrence after hormone reduction. IVIG and plasma exchange can shorten the time of mechanical ventilation in patients with MG crisis, and are often used in patients with life-threatening MG. For patients with thymoma, thymectomy can also be performed when their condition is stable. Giant cell

myocarditis is the most serious manifestation of MG myocarditis. Older patients with larger thymoma are more likely to develop giant cell myocarditis (Sasaki et al., 2012).

van Haelst et al. (2006) found that the symptoms and myocardial inflammation of patients with giant cell myocarditis were improved after treatment, and no multinucleated giant cell myocardial infiltration was found after 6 months of treatment. Fayssoil et al. (2010) revealed that patients with refractory heart failure caused by giant cell myocarditis were treated with ECMO for 7 days without immunosuppressant therapy, and then the cardiac function was significantly improved, which suggests that giant cell myocarditis may be self-limited and the supportive treatment techniques such as ECMO can help patients tide over the difficulty. Even with high-dose methylprednisolone, tacrolimus, IVIG, plasma exchange, endotracheal intubation, and severe cardiac support, the effect was still not obvious. Myositis may either occur concurrently with, or precede the development of, MG. Conversely, myocarditis always seems to follow MG (Shah et al., 2015). Importantly, a previous study found that myositis and/or myocarditis occur concomitantly with MG, and are frequently related to poor outcomes (Fuentes-Antrás et al., 2020). There were 35 cases of MG complicated with myocarditis in our review, and the death group accounted for 57.14% (20/35). The specific causes of death of the 20 patients are as follows (representing the number of cases): refractory thymoma (4) (Hyun et al., 2020; Sasaki et al., 2012; Suzuki et al., 2014; Tanahashi et al., 2004); cardiac and respiratory insufficiency (4) (Konstantina et al., 2019; Namba et al., 1974; Shintaku et al., 2017; Suzuki et al., 2014); myasthenia crisis (3) (Kon et al., 2013; Suzuki et al., 2014); the possible delay to diagnosis (2) (HooKim et al., 2008; Takai et al., 2020); multiple organ failure (1) (Joudinaud et al., 2006); worsening kidney function with hyperkalemia and severe metabolic acidosis (1) (Jeyakumar et al., 2020); poor tolerance to treatment and the patient expressed desire to cease aggressive therapy (2) (Fazel & Jedlowski, 2019; Fuentes-Antrás et al., 2020); progression of the primary malignant tumor (2) (Valenti-Azcarate et al., 2020; Vermeulen et al., 2020); and cumulative diaphragm with myositis (1) (Priemer et al., 2018). Our review shows over 30% cases of myocarditis occurred concomitantly with MG, which may provide a further explanation for over half of the deaths.

However, our study has the limitation that this review excludes articles published in non-English, which may lead to language bias. However, we also screened articles published in languages other than English in the database, and found no other abstracts that met the criteria for this review.

5 | CONCLUSION

It is further suggested that the prognosis of patients with MG complicated with myocarditis is poor, and myocardial enzymes and other indexes need to be monitored for patients taking ICI drugs. Patients with dyspnea who are still not ideally treated by mechanical ventilation should be vigilant against the occurrence of MG complicated with myocarditis.

AUTHOR CONTRIBUTIONS

Wei Chen and Min Yang selected the studies. Wei Chen and Min Yang wrote the manuscript. Wei Chen, Tian Sun, Cong Liu, Zijing Zhou, Jianxi Duan, Yiyang Zhao, Min Yang and Pin Chen reviewed and helped writing the manuscript. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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