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ORIGINAL RESEARCH

Immune Checkpoint Inhibitor Associated Myopathy with Concurrent Myocardial Injury: A Retrospective Cohort Study

Lipeng Yang, Xiuli Li, Jing Zhang, Xinhong Feng

Department of Neurology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua Medicine, Tsinghua University, Beijing, 102218, People's Republic of China

Correspondence: Xinhong Feng, Department of Neurology, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua Medicine, Tsinghua University, Litang Road 168#, Beijing, 102218, People's Republic of China, Tel/Fax +8613720085706, Email fxha01071@btch.edu.cn

Objective: To characterize immune checkpoint inhibitor (ICI) myopathy complicated by myocardial injury.

Methods: Retrospective analysis of 16 patients who were diagnosed with ICI myopathy complicated by myocardial injury at Beijing Tsinghua Changgung Hospital from 2020 to 2025.

Results: The cohort comprised 16 patients (male:female ratio: 10:6; mean age 68 years) who developed at a median of 37 days after the initial immunotherapy. The initial clinical manifestations included ptosis in 43.8% (n=7) of the patients, bulbar muscle involvement in 12.5% (n=2), and respiratory muscle impairment in 18.8% (n=3). All patients demonstrated cardiac involvement. Laboratory findings revealed elevated creatine kinase (CK) levels (mean 2190.9 U/L), CK-MB isoenzyme (mean 79.1 ng/mL) and high-sensitivity troponin T levels (hs-TnT) (mean 1.077 ng/mL) in all patients. Anti-acetylcholine receptor antibody positivity was observed in 25% (1/4) and anti-titin antibody positivity in 50% (2/4) of the tested patients. Myopathic changes were identified in 50% of patients (3/6), and one patient exhibited a decremental response to low-frequency repetitive nerve stimulation with an incremental response to high-frequency stimulation. During the course of hormone therapy, we observed a previously unreported discordant phenomenon in 50% of patients (n=8), characterized by a rebound elevation in the CK-MB isoenzyme occurring concurrently with a gradual decline in total CK levels.

Conclusion: ICI myopathy is a distinct immune-mediated disorder that emerges following cancer immunotherapy. It is characterized by skeletal and cardiac muscle involvement, with a hallmark clinical feature of nonfluctuating ptosis. It is particularly noteworthy that even patients presenting with mild clinical symptoms and only minor elevations in CK or cardiac enzymes should be carefully evaluated for electrocardiographic abnormalities and monitored for malignant arrhythmias. Early diagnosis, prompt intervention, and rigorous monitoring of laboratory parameters and cardiac rhythms during the acute phase are essential for improving outcomes.

Keywords: immune checkpoint inhibitors, PD-1, ptosis, myopathy, myocarditis

Introduction

Immune checkpoint inhibitors (ICIs), including cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), and lymphocyte activation gene 3 (LAG-3), have emerged as pivotal agents in cancer immunotherapy.[1] However, their expanding use has revealed a spectrum of immune-related adverse events (irAEs). Neurological irAEs, accounting for 1–3% of all irAEs,[2,3] encompass conditions such as Guillain-Barré syndrome, myasthenia gravis, and myopathies. Recent reports highlight PD-1/PD-L1 inhibitor-associated myopathy with distinctive clinical features, including ptosis as a frequent initial symptom and concurrent myocarditis in approximately 32% of cases.[4] Histopathologically, these myopathies are characterized by multifocal clusters of necrotic and regenerating muscle fibres, distinguishing them from other autoimmune myopathies.[5]

Myasthenia gravis (MG) and ICI-induced myopathy can both present with ptosis, dysarthria, and limb weakness, making their differentiation challenging. Furthermore, MG-specific antibodies may also test positive in a subset of

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patients with ICI myopathy. ICI-induced MG typically manifests as fluctuating muscle weakness without myalgia or muscle pain, a feature that may aid in distinguishing it from ICI myopathy. However, it should be noted that concurrent myopathy and MG following ICI therapy is not uncommon.[6]

ICI-related cardiovascular adverse events are rare, occurring in approximately 1% to 1.5% of patients treated with immune checkpoint inhibitors, yet they can be fatal, with an estimated mortality rate of up to 50% for myocarditis.[7] The pathological diagnostic criteria for ICI-associated myocarditis are "multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy." The 2022 ESC Cardio-Oncology Guidelines[8] were the first to propose a clinical diagnosis for ICI-associated myocarditis, which is centred on troponin elevation (new or significant change from baseline). After excluding acute coronary syndrome (ACS) and acute infectious myocarditis on the basis of clinical suspicion, the diagnosis can be established by meeting one major criterion-CMR diagnostic for acute myocarditis (modified Lake Louise criteria) or two minor criteria, which include: (1) clinical syndrome; (2) ventricular arrhythmia and/or new conduction system disease; (3) decline in left ventricular systolic function, with or without regional wall motion abnormalities in a non-Takotsubo pattern; (4) other immune-related adverse events, particularly myositis, myopathy, or myasthenia gravis; and (5) CMR suggestive of myocarditis.

Despite growing recognition of this condition, clinical studies on ICI myopathy remain scarce and are limited predominantly to case reports. This study retrospectively analysed the clinical characteristics and management of 16 patients with ICI myopathy complicated by myocardial injury, aiming to increase clinical awareness and provide diagnostic and therapeutic insights for this underrecognized condition.

Materials and Methods

Study Population

We retrospectively analysed 16 patients who were diagnosed with ICI myopathy complicated by myocardial injury at Beijing Tsinghua Changgung Hospital from August 2020 to January 2025. Detailed clinical data, including medical history, neurological symptoms/signs, and laboratory findings, were collected. The inclusion criteria were as follows: (1) prior ICI therapy; (2) elevated serum creatine kinase (CK) and CK-MB isoenzyme levels; (3) muscle weakness and/or cardiac symptoms supported by objective evidence (physical examination, electrocardiography, electromyography, or muscle MRI); and (4) exclusion of alternative causes of myopathy. This retrospective cohort study was approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (Approval No. 25323-6-01).

Clinical Data

Demographic and clinical parameters were collected. Disease severity was graded per the Society for Immunotherapy of Cancer (SITC) consensus criteria,[9] adapted from the Common Terminology Criteria for Adverse Events (CTCAE): CTCAE grade 1 (mild) includes patients with paucisymptomatic hyperCKemia and/or myalgia without weakness. Grade 2 (moderate) encompasses mild-moderate weakness (including ocular weakness) of the Medical Research Council (MRC) grades 4 to 4+. Grade 3 (severe) includes moderate-severe limb/neck weakness, impaired ambulation or requirement of a gait aid, dysphagia requiring dietary modification, and/or dyspnoea without requiring noninvasive/invasive ventilation. Grade 4 (fulminant) includes patients requiring intubation/noninvasive ventilation and/or feeding tube placement for dysphagia. Grade 5 is assigned for death attributable to respiratory failure and/or bulbar weakness.

Biological Data

We collected peak serum levels and longitudinal changes in CK, CK-MB, myoglobin (MYO), and high-sensitivity troponin T (hs-TnT) for all patients during the follow-up course, along with lymphocyte subset profiles in a subset of patients. Additionally, we compiled autoimmune antibody laboratory results, myositis-associated antibodies and myasthenia gravis-related antibodies from selected patients.

Neurophysiological Examinations

Experienced neurologists used the Nicolet EDX electromyography system (Natus Medical Incorporated, USA), and selected patients underwent nerve conduction Studies (NCSs), needle electromyography (nEMG), and repetitive nerve stimulation (RNS).

Additional Evaluations

Electrocardiograms (GE MAC 5500, USA) and echocardiograms (GE Vivid E9, USA) were obtained for all patients at disease onset. A subset of patients underwent bilateral thigh muscle and cardiac magnetic resonance imaging (MRI) using a 3.0 T MRI scanner (GE Healthcare, USA).

Statistical Analysis

Data were analysed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Intergroup comparisons were performed by Mann–Whitney *U*-test with statistical significance defined as $p < 0.05$.

Results

Demographic and Clinical Characteristics

The study included 16 patients with a mean age of 68 years at onset and a male predominance (male:female = 10:6). The primary malignancies included hepatocellular carcinoma (n=6), cholangiocarcinoma (n=2), intrahepatic cholangiocarcinoma (n=1), gastric cancer (n=1), urothelial carcinoma (n=1), renal cell carcinoma (n=1), lung cancer (n=1), colon cancer (n=1), pancreatic cancer (n=1), and uterine cancer (n=1).

The ICI types included PD-1 inhibitors in 13 patients (pembrolizumab, n=4; tislelizumab, n=4; sintilimab, n=4; camrelizumab, n=1), PD-L1 inhibitors in 2 patients (durvalumab, n=1; atezolizumab, n=1), and a dual PD-1/CTLA-4 inhibitor (cadonilimab) in 1 patient. ICI myopathy developed at a median of 37 days (range: 14–231 days) after the first ICI dose. Among these patients, 43.8% (n=7) developed symptoms after the second ICI cycle, 31.3% (n=5) after the first cycle, with a median onset at cycle 2 (range: 1–10).

Clinically, 43.8% (n=7) presented with ptosis as the initial symptom, 37.5% (n=6) with fatigue, 6.3% (n=1) with neck weakness, and 12.5% (n=2) with chest tightness. Bulbar muscle involvement was observed in 12.5% (n=2) of patients, respiratory muscle involvement in 18.8% (n=3), and myocardial involvement in all patients (n=16), manifesting as chest tightness. A reduced left ventricular ejection fraction occurred in 18.8% (n=3) of patients, and malignant arrhythmias occurred in 12.5% (n=2) of patients.

The clinical data and statistical analyses for all patients are presented in Table 1 and Table S1.

Laboratory Findings

All patients presented elevated levels of CK and cardiac enzymes. The mean serum CK level was 2190.9 U/L (range: 388.0–7116.0 U/L), with the average CK-MB isoenzyme level being 79.1 ng/mL (10.3–204.0 ng/mL). hs-TnT levels was elevated to a mean of 1.077 ng/mL (0.026–4.030 ng/mL), and MYO levels increased to a mean of 1342.4 ng/mL (130.0–4157.0 ng/mL). Interleukin-6 (IL-6) levels were measured in 7 patients, with a mean value of 17.67 pg/mL (range: 1.47–44.73 pg/mL). Among the patients who underwent testing, 62.5% (5/8) tested positive for antinuclear antibodies (ANAs), 12.5% (1/8) were positive for anti-SSA/Ro and anti-SSB/La antibodies, 25% (1/4) were positive for anti-acetylcholine receptor (AChR) antibodies, and 50% (2/4) tested positive for anti-titin antibodies. Two patients were positive for anti-heart antibodies. Among the 5 patients evaluated for myositis-specific antibodies, one was positive for PM-Scl100, and the other was positive for Ro-52.

Lymphocyte subset analysis was performed for 9 patients. Five patients were tested prior to glucocorticoid administration, with a mean testing time of 37.2 days (range: 16–47 days) after initiating immune checkpoint inhibitor (ICI) therapy. The mean CD4+ T-cell count was 331.908 cells/μL (range: 68–499.09 cells/μL), the CD8+ T-cell count was 272.09 cells/μL (range: 36–684.4 cells/μL), and the CD4/CD8 ratio was 1.850 (range: 0.54–4.03). The remaining 4 patients were tested within 2–4 days after glucocorticoid initiation, with a mean CD4+ T-cell count of 325.855 cells/μL

Table 1 Clinical Data Summary

Average Age (Years)	**68**	**Neuroelectrophysiology**	
Gender		RNS decreases at low frequencies	1/5 (20.0%)
Male	10 (62.5%)	NCV normal	5/5 (100.0%)
Female	6 (37.5%)	Myopathic changes of NEMG	3/4 (75.0%)
Initial symptom		**Thigh muscle MRI oedema**	2/2 (100.0%)
Ptosis	7 (43.8%)	**ECG**	
Fatigue	6 (37.5%)	BBB	8/16 (50.0%)
Weakness in the neck	1 (6.3%)	1 AVB	3/16 (18.8%)
Chest distress	2 (12.5%)	Abnormal ST-T	5/16 (31.3%)
Involved site		New-onset sinus bradycardia	4/16 (25.0%)
Eye	8 (50%)	QTc interval prolonged	4/16 (25.0%)
Bulbar	2 (12.5%)	Ventricular pre-excitation	1/16 (6.3%)
Limbs	9 (56.3%)	**UCG**	
Neck	1 (6.3%)	Abnormal segmental movement of the left ventricular wall	2/16 (12.5%)
Respiratory muscle	3 (18.8%)	The left ventricular ejection fraction decreased	3/16 (18.8%)
Myocardium	16 (100.0%)	The diastolic function declines	7/16 (43.8%)
Median time from first ICI to onset (days)	37 (14–231)	**Treatment**	
Median treatment course (cycles)	2 (1–10)	Pulse steroid therapy	13/16 (81.3%)
ICI type		Gamma globulin	8/16 (50.0%)
PD-1 inhibitor		Plasma exchange	1/16 (6.3%)
P	4 (25.0%)	Immunosuppressant	3/16 (18.8%)
T	4 (25.0%)	Invasive mechanical ventilation	3/16 (18.8%)
S	4 (25.0%)	Pacemaker implantation	2/16 (12.5%)
Cr	1 (6.3%)	**Prognosis**	
PD-L1 inhibitor		Improved and discharged from the hospital	14/16 (87.5%)
D	1 (6.3%)	Death	2/16 (12.5)
A	1 (6.3%)	Average time from steroid therapy to improvement (days)	14.7 (1–40)
PD-1/CTLA-4 dual-channel inhibitor		Median time from onset to improvement (days)	30 (10–149)
Cd	1 (6.3%)		
CK mean value (U/L)	2190.9 (388.0–7116.0)		
CK-MB mean value (ng/mL)	79.1 (10.3–204.0)		
hs-TnT mean value (ng/mL)	1.077 (0.026–4.030)		

Abbreviations: ICI, immune checkpoint inhibitor; P, pembrolizumab; T, tislelizumab; D, duvalizumab; A, atezolizumab; Cr, camrelizumab; S, sindelizumab; Cd, camrelizumab; CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; hs-TnT, high-sensitivity troponin T; RNS, repetitive frequency electrical stimulation; NCV, nerve conduction; NEMG, needle electromyography; ECG,electrocardiogram; UCG, echocardiography; BBB, bundle branch block; 1 AVB,first-degree atrioventricular block.

(range: 113.96–506.85 cells/μL), a CD8+ T-cell count of 247.55 cells/μL (range: 88–502.41 cells/μL), and a CD4/CD8 ratio of 1.757 (range: 0.77–3.38).

CK and CK-MB Temporal Trends

During the treatment course, 50.0% (8/16) of patients demonstrated a gradual decline in CK levels, whereas the CK-MB isoenzyme level initially decreased but then rebounded. The median time to CK-MB rebound occurred on Day 6 (range: 4–13) after treatment initiation, with postrebound peak levels averaging 36.1 ng/mL (12.5–53.5 ng/mL), reaching 47.3% (31.9–63.3%) of the initial peak values observed at disease onset. Four patients showed concurrent rebounds in both CK and CK-MB, two patients exhibited sustained decreases in both markers to normal ranges, one deceased patient displayed persistent increases in CK and CK-MB, and another deceased patient showed declining trends without normalization. The discordant kinetic patterns between CK and CK-MB in these patients are illustrated in Figure 1. The MYO trends paralleled those of CK, while hs-TnT mirrored CK-MB but with heightened sensitivity.

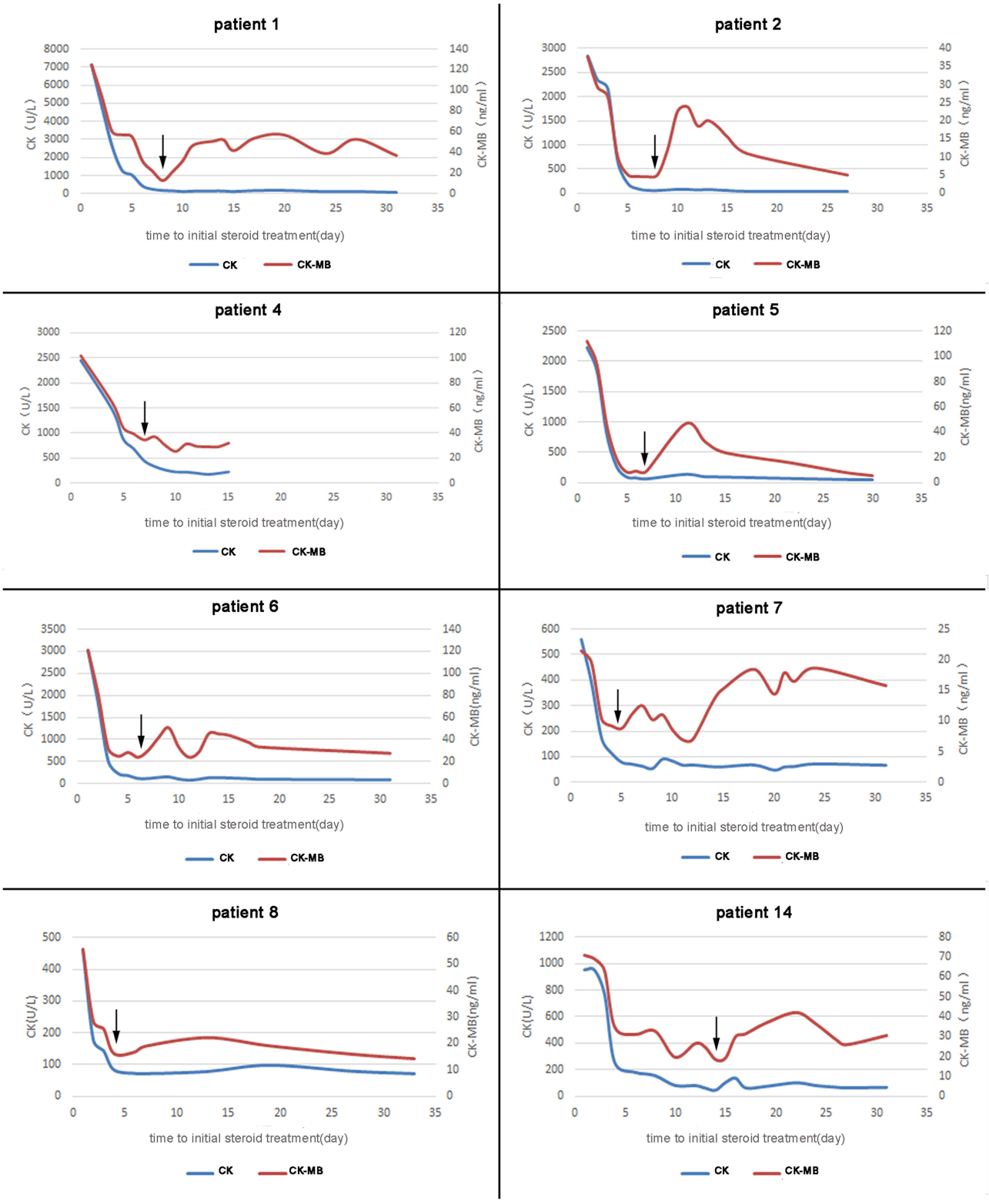

Figure 1 Temporal Trends of CK and CK-MB. A discordant pattern of declining CK with rebound elevation of CK-MB was observed in 8 patients. The blue and red lines represent the CK and CK-MB trends, respectively. The black arrows indicate the onset of CK-MB rebounds.

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Statistical Comparisons

Patients were stratified according to age, sex, ICI type, number of treatment cycles, initial symptoms, muscle strength, respiratory muscle involvement, and clinical outcome. The patients who developed symptoms within 1–3 ICI cycles had significantly higher CK-MB (p = 0.002,) and hs-TnT (p = 0.002) levels than did those with symptoms after ≥4 cycles.

The patients with limb muscle strength MRC grade≤4 presented higher CK-MB levels than did those with grade 5/5− (p= 0.017). Respiratory muscle involvement was associated with elevated CK-MB (p = 0.039). hs-TnT levels were significantly higher in patients who died than in survivors (p = 0.017). Patients with ptosis had significantly higher CK-MB levels than those without ptosis (p = 0.028).

No other intergroup differences reached statistical significance (Table 2).

Neurophysiological Studies

Six patients underwent RNS studies. Five patients presented normal findings, while one patient presented a low-frequency decrease (3 Hz, amplitude decline to 15%) in the facial nerve and a high-frequency increase (20 Hz, amplitude increase to 106%) in the ulnar nerve during the six-month follow-up. Five patients underwent NCSs, all of which revealed no abnormalities. Four patients underwent nEMGs, with three demonstrating myopathic changes (short-duration polyphasic motor unit action potentials with reduced recruitment) and one showing normal findings. Needle EMG revealed fibrillation potentials and positive sharp waves at rest in the following muscles: the bilateral deltoids, biceps brachii, vastus medialis, tibialis anterior, sternocleidomastoids, and T10-T11 paraspinal muscles. During mild contraction, short-duration polyphasic motor unit action potentials with a reduced duration were observed.

Electrocardiographic and Echocardiographic Findings

A total of 50% of patients (8/16) exhibited bundle branch block on electrocardiogram (ECG), including 2 patients with pre-existing right bundle branch block (RBBB), 4 patients with newly developed complete RBBB, 1 patient with left anterior fascicular block, and 1 patient with intraventricular conduction delay; 18.8% (3/16) had first-degree atrioventricular (AV) block, 31.3% (5/16) demonstrated ST-segment elevation or depression, 25.0% (4/16) exhibited newly developed sinus bradycardia, 25.0% (4/16) displayed QTc prolongation, and 6.25% (1/16) had ventricular pre-excitation. (The patients' ECG is shown in Figure S1).

In one deceased patient, the ECG on Day 5 of illness revealed significant abnormalities, including sinus tachycardia, ventricular premature contractions (VPCs), intraventricular conduction delay, wide QRS complexes, complete RBBB, and QTc prolongation (584 ms). Two days later, the ECG further deteriorated, showing ST-segment changes, incomplete interference AV dissociation, and QTc prolongation to 601 ms. Another deceased patient with a pre-existing dual-chamber pacemaker for cardiomyopathy demonstrated bidirectional ventricular tachycardia on Day 5 of illness (ECG tracings of both cases are shown in Figure 2).

On echocardiography, 43.8% of patients (7/16) exhibited diastolic dysfunction, 12.5% (2/16) showed left ventricular (LV) regional wall motion abnormalities, and 18.8% (3/16) had a reduced LV ejection fraction (LVEF, 30–38%). Among the three patients with a reduced LVEF, two died during hospitalization, and one died one year post-discharge due to multiorgan failure secondary to metastatic malignancy (Table S2).

Two patients underwent speckle-tracking echocardiography. In Patient 6, the global longitudinal strain (GLS) was –20.3%, which was within normal limits. In Patient 8, the GLS was –14.6%, indicating reduced left ventricular systolic function (Table S1).

Muscle and Cardiac MRI

Muscle MRI in 2 patients revealed oedema signals in the bilateral thigh muscles (Figure 3).

Cardiac MRI was performed in three patients, revealing crescentic late gadolinium enhancement (LGE) in the inferoseptal and mid inferior left ventricular segments in Patient 7, apical T2WI hyperintensity with patchy mid myocardial LGE in the mid inferior left ventricular wall in Patient 8, and subepicardial LGE in the inferior left ventricular wall in Patient 12 (Table S1).

Table 2 Comparison of the Mean Levels of CK, CK-MB, and Hs-TnT Across Different Groups

	n	CK (U/L)	p	U	CK-MB (ng/mL)	p	U	hs-TnT (ng/mL)	p	U
Age of onset										
≥70 years	5	2448.0 (970.5, 4139.5)	0.510	34	70.8 (24.6, 160.0)	0.827	30	0.36 (0.13, 2.30)	0.827	25
<70 years	11	1681.0 (460.0, 3014.0)			55.8 (21.5, 121.0)			0.57 (0.06, 1.62)		
Gender										
Male	10	2101.0 (1122.3, 3747.6)	0.428	22	99.0 (24.6, 145.3)	0.368	21	1.13 (0.05, 3.05)	0.428	22
Female	6	970.5 (533.5, 2885.0)			46.7 (19.0, 83.4)			0.38 (0.18, 0.65)		
ICI type										
PD-1/dual-channel	14	1717.0 (533.5, 3056.6)	0.817	16	52.5 (20.7, 114.1)	0.150	24	0.38 (0.05, 1.74)	0.417	20
PD-L1	2	2064.5 (1681.0,2064.5)*			156.0 (116.0,156.0)*			1.25 (0.88, 1.25)*		
ICI treatment course										
1 to 3 cycles	12	2064.5 (657.0, 3141.9)	0.379	16	99.0 (50.8, 126.6)	0.002	1	0.89 (0.37, 2.53)	0.002	1
≥4 cycles	4	1534.0 (537.8, 2111.0)			15.0 (10.6, 24.6)			0.04 (0.03, 0.14)		
Symptom										
Ptosis	8	2645.0 (1135.8, 4831.3)	0.105	48	118.5 (45.9, 179.1)	0.028	53	0.73 (0.37, 2.53)	0.161	46
Non-ptosis	8	1170.0 (437.5, 2111.0)			37.9 (13.3, 78.5)			0.11 (0.03, 1.25)		
Muscle strength										
MRC grades 5-/5	14	1717.0 (533.5, 2885.0)	0.417	20	52.5 (20.7, 112.9)	0.017	28	0.38 (0.05, 1.02)	0.100	25
MRC grades 4 and below	2	3559.0 (1681.0,3559.0)*			200.0 (196.0, 200.0)*			2.67 (1.62, 2.67)*		
Respiratory muscles										
Involved	3	2448.0 (1681.0,2448.0)*	0.239	29	128.4 (116.0, 128.4)*	0.039	35	1.62 (0.88, 1.62)*	0.146	31
Not involved	13	1353.0 (509.0,2928.0)			49.1 (20.0, 99.0)			0.36 (0.05, 1.14)		
Outcome										
Death	2	2933.5 (430.0, 2933.5)*	1.000	14	145.1 (86.1, 145.1)*	0.200	23	3.87 (3.71, 3.87)*	0.017	28
Improved	14	1881.0 (855.0,2885.0)			52.5 (20.7, 117.3)			0.38 (0.05, 1.02)		

Notes: *P* values were derived from Mann–Whitney *U*-test. Data are presented as median (IQR), *Data are presented as median (range) for subgroups with n < 4.

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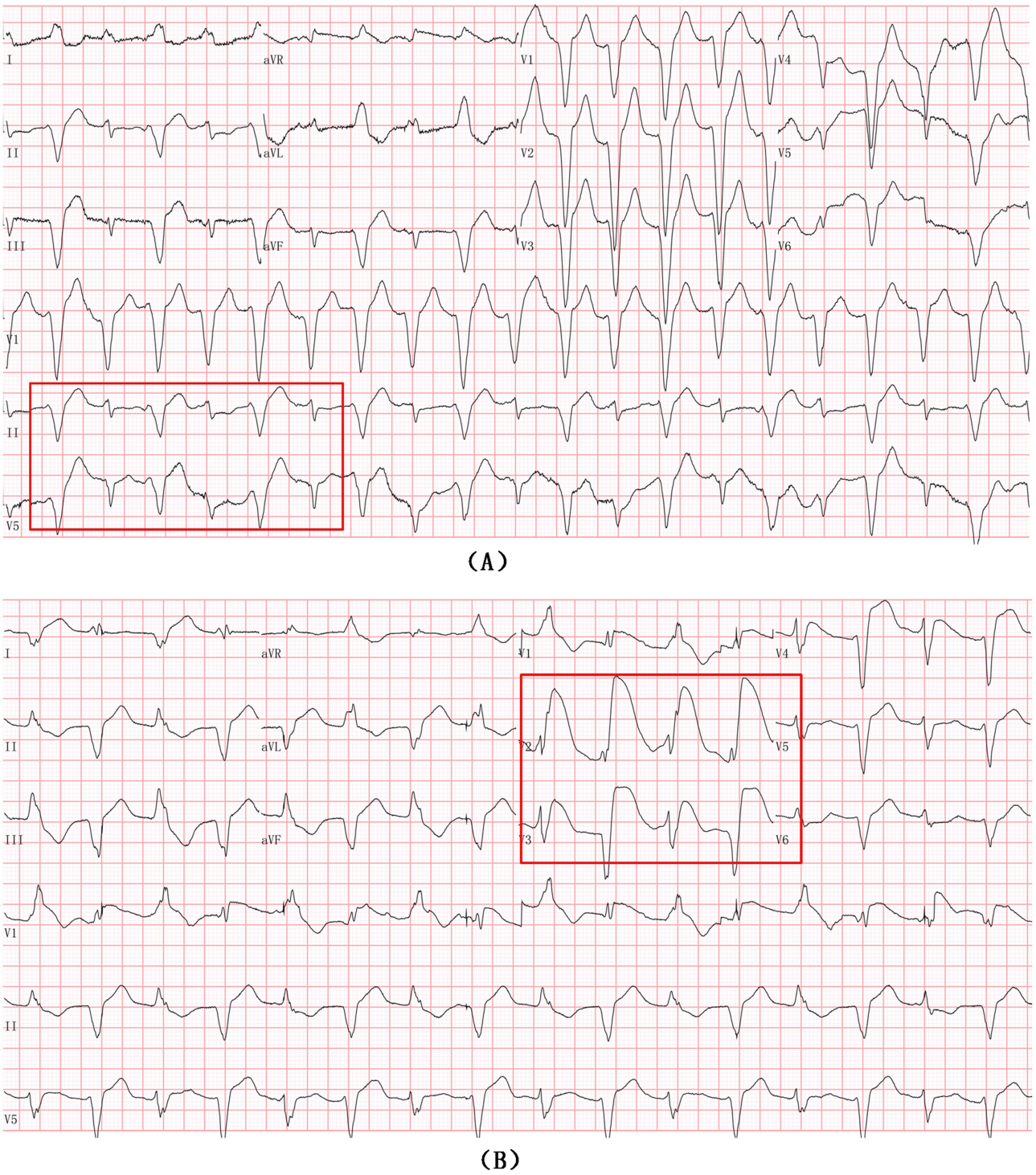

Figure 2 Representative Electrocardiograms. (**A**) ECG of Patient 10 on admission showed tachycardia, ventricular premature beats, and broad QRS complexes (highlighted by red boxes). (**B**) ECG of Patient 11 on admission demonstrated broad QRS complexes and ST-segment elevation (highlighted by red boxes).

Coronary Computed Tomography Angiography (CTA) and Coronary Angiography

Two patients underwent coronary CTA. In Patient 2, mild atherosclerotic changes were observed in the coronary arteries without significant stenosis. In Patient 13, a calcified plaque was identified in the left main coronary artery, with mild luminal narrowing.

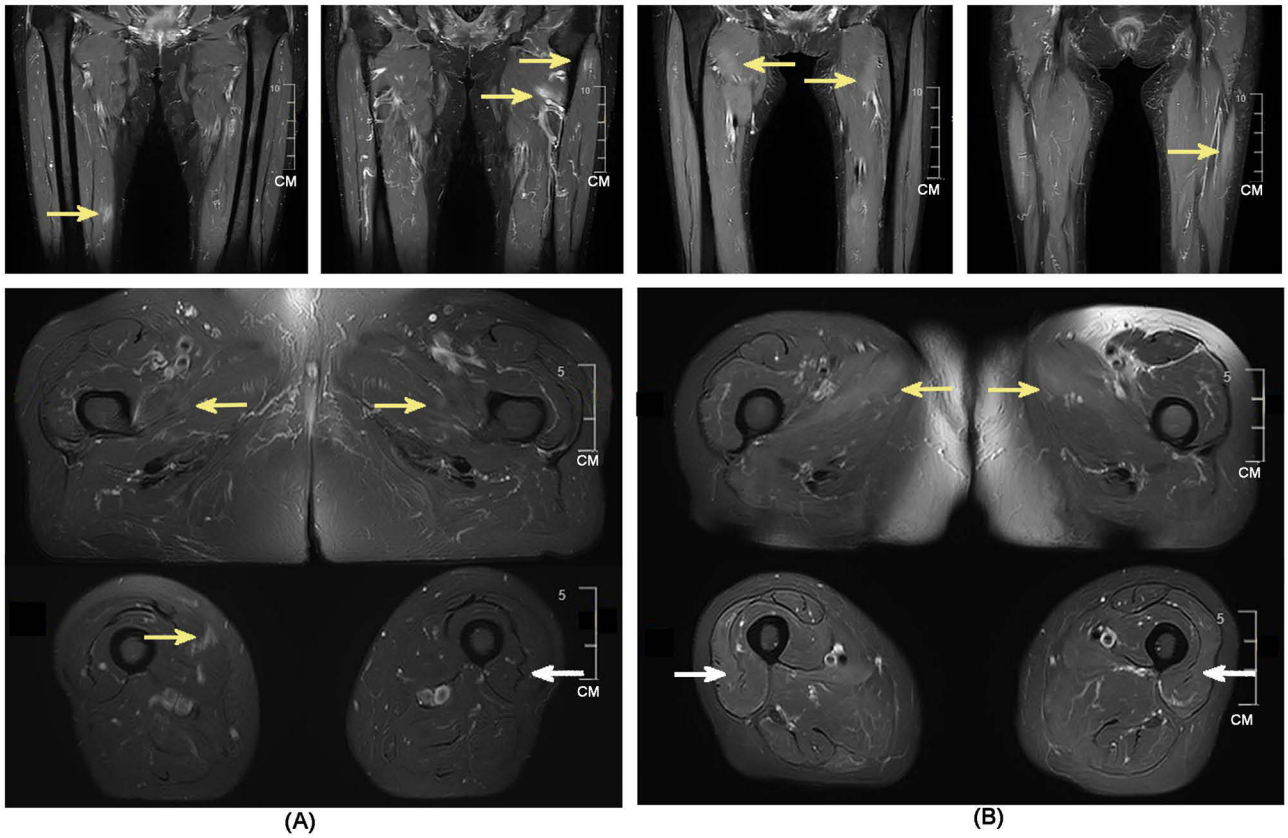

Figure 3 Thigh MRI T2-Weighted Fat-Suppressed Sequences (**A**) Patient 2: Axial view demonstrates patchy hyperintensities in the quadriceps femoris, more prominent on the left side (yellow arrows), with M-shaped fascial changes (white arrows). CM, centimeter. (**B**) Patient 6: Axial view reveals bilateral quadriceps femoris with roughly symmetrical patchy hyperintensities (yellow arrows) and M-shaped fascial changes (white arrows). CM, centimeter.

Patient 11 underwent coronary angiography, which indicated moderate stenosis of 30–40% in the middle segment of the left anterior descending branch and 30% stenosis in the middle segment of the right coronary artery (Table S1).

Treatment and Outcomes

All 16 patients received steroid therapy. Patients with symptom onset after ≥4 ICI cycles required significantly lower cumulative methylprednisolone doses in the first 5 days compared with those with symptom onset within 1–3 cycles (555.0 mg vs. 2319.5 mg, $p = 0.015$).

Eight patients (50.0%) received intravenous immunoglobulin (IVIg), one patient underwent plasma exchange, 3 required mechanical ventilation, 2 received temporary pacemakers, and 3 were treated with immunosuppressants (mycophenolate mofetil).

Fourteen patients improved and were discharged, with a mean time to initial improvement (defined by subjective and objective measures) of 14.7 days (median: 11.5 days; range: 1–40) post-steroid initiation, corresponding to a median of 30 days (10–149) post-symptom onset. CK normalization occurred at a median of 5 days (2–35) post-treatment. Patients with CK-MB rebound had a median time from steroid initiation to discharge of 9 days, versus 12 days for those without rebound ($p = 0.755$, $U = 21$), with no statistically significant difference.

One patient died of metastatic cancer-related multiorgan failure at the 1-year follow-up. Two fatalities occurred during hospitalization on Day 8 due to malignant arrhythmias.

The treatment protocols and outcomes are detailed in Table 3.

Table 3 Treatment Regimens and Clinical Outcomes

No.	Days from Onset to Steroid Initiation	Steroid Regimen	IVIg	Additional Therapies	Outcome	Days from Treatment to Improvement/ Discharge	Days from Onset to Death
1	7	Methylprednisolone 500 mg ×3 d, tapered	1 course	PE, IMV	Improved; died 1 year later (metastatic cancer)	26	
2	5	Methylprednisolone 500 mg ×5 d →65 mg	None		Improved and discharged	20	
3	10	Methylprednisolone 1 g ×6 d →500 mg ×1 d →70 mg	2 courses	IS	Improved and discharged	23	
4	14	Methylprednisolone 500 mg ×3 d →80 mg	1 course	IMV	Improved and discharged	13	
5	14	Methylprednisolone 1 g ×3 d, tapered	1 course		Improved and discharged	6	
6	6	Methylprednisolone 500 mg ×5 d, tapered	None	IS, TPM	Improved and discharged	4	
7	10	Methylprednisolone 500 mg ×4 d, tapered	1 course		Improved and discharged	28	
8	4	Methylprednisolone 500 mg ×3 d →60 mg	1 course (3 d)		Improved and discharged	6	
9	7	Methylprednisolone 24 mg ×3 d →16 mg	None		Improved and discharged	40	
10	5	Methylprednisolone 500 mg ×3 d	None		Died (malignant arrhythmia)		8
11	2	Methylprednisolone 500 mg ×5 d	1 course (2 d)		Died (malignant arrhythmia)		8
12	38	Prednisone 100 mg ×2 d	None		Improved and discharged	1	
13	3	Prednisone 80 mg ×3 d →40 mg	None		Improved and discharged	14	
14	14	Steroid 500 mg ×4 d	1 course (8 d)	IS, TPM	Improved and discharged	6	
15	34	Methylprednisolone 250 mg ×3 d, tapered	None		Improved and discharged	9	
16	139	Methylprednisolone 80 mg ×7 d	None		Improved and discharged	10	

Abbreviations: IVIg, intravenous immunoglobulin; d, day or days; PE, lasma exchange; IMV, invasive ventilation; IS, immunosuppressants; TPM, temporary pacemaker.

Discussion

In this study summarizing the clinical characteristics and management of 16 patients with ICI-related myopathy complicated by myocardial injury, we observed a male predominance and a mean age of onset of 68 years. Approximately three-fourths of the cases occurred within the first two cycles of ICI therapy. We found that patients with later-onset disease demonstrated milder clinical manifestations. Those who developed symptoms after the fourth ICI cycle had significantly lower CK-MB levels than those with onset during cycles 1–3, received lower initial steroid doses within the first five days, and experienced no mortality.

Previous studies reported that ICI myopathy typically presents acutely or subacutely at a median of the second treatment cycle, with wide variability in onset timing—some cases even manifesting after more than 20 cycles.[2,10,11] Our

findings are consistent with those previously reported, and we further discovered that the patients with later-onset disease demonstrated milder clinical manifestations.

While CK elevation (>5× upper limit of normal) is common in ICI myopathy, normal CK levels have been documented in biopsy-proven cases.[5,11–13] We found that CK levels were poorly correlated with clinical weakness, while CK-MB and hs-TnT were strongly associated with disease severity and prognosis. These findings align with those of a multicentre study of 35 patients with ICI-induced myocarditis, in which patients who experienced major adverse cardiovascular events (MACE, defined as cardiovascular death, cardiogenic shock, cardiac arrest, or complete heart block) had significantly higher troponin T levels at admission, peak, and before discharge. A troponin T level ≥1.5 ng/mL measured before discharge or at the final assessment was associated with a four-fold increased risk of MACE.[14]

Prior studies have reported higher CK levels in ICI-induced myopathy patients with ocular muscle involvement;[5,13] however, other studies have reported normal CK levels in 50% of biopsy-confirmed cases involving ocular muscles.[9] In our cohort, patients with ptosis had higher median CK levels than those without ptosis (2645.0 U/L vs 1170.0 U/L), though the difference was not statistically significant, whereas CK-MB levels were significantly elevated in patients with ptosis. Overall, existing studies remain limited by small sample sizes, necessitating larger cohorts to confirm these differences. For patients with ptosis-predominant presentations and normal CK levels, early differentiation from myasthenia gravis poses diagnostic challenges and requires the exclusion of alternative aetiologies owing to divergent therapeutic strategies.

We observed that, following initiation of corticosteroid therapy, approximately half of the patients exhibited a gradual decline in CK levels, accompanied by an initial decrease, which was subsequently followed by a rebound in CK-MB and hs-TnT levels (median time to rebound occurring on day 6 after treatment initiation)—a previously unreported discordant phenomenon. The decline in CK may indicate a rapid and favorable therapeutic response of myopathy to steroid treatment, whereas the rebound of CK-MB and hs-TnT often raises clinical concern: does it suggest disease relapse, and should steroid tapering be delayed or dosage be escalated? We reviewed the electrocardiograms and clinical symptoms of patients at the time of CK-MB and hs-TnT rebound; most patients did not show significant symptom worsening or notable ECG changes. Retrospective chart review revealed that the pace of steroid tapering was slowed in several patients due to the cardiac enzyme rebound; however, there was no significant difference in the time to symptom improvement/discharge between patients with and without such enzyme rebound. Owing to the limitations inherent in a retrospective study, we are unable to provide a satisfactory explanation for this phenomenon. Nevertheless, it is noteworthy that myopathy with concomitant myocarditis carries a mortality rate as high as 50%,[10,15,16] warranting heightened clinical vigilance. We believe that continuous monitoring of cardiac enzymes is essential for patients with ICI-associated myopathy and myocardial injury, particularly during the first two weeks of treatment; when fluctuations in cardiac enzymes occur, further assessments such as electrocardiography and GLS should be considered. Future larger-scale cohort studies are needed to further investigate the dynamic evolution of these biomarkers and to evaluate their clinical significance.

Prior studies have linked peripheral blood lymphocyte profiles to severe irAEs, demonstrating that elevated CD4+ effector memory T (TEM) cells and TCR clonality in blood samples collected within 3 months of ICI initiation are correlated with severe irAE development.[17] Furthermore, CD8+CD28+ T-cell levels have been associated with both ICI therapeutic response (median 236 vs 138 cells/μL in responders vs nonresponders, $p < 0.001$) and grade 3–4 irAEs, with a threshold of ≥309 cells/μL.[18] In our study, longitudinal comparisons post-steroid therapy revealed variable CD4+/CD8+ T-cell trends (both increasing and decreasing). Large-scale randomized controlled studies are warranted to elucidate the role of lymphocyte dynamics in ICI myopathy pathogenesis and management.

Early-stage ICI myopathy requires differentiation from myasthenia gravis (MG), another neurological irAE of ICI therapy. Typical clinical manifestations of ICI-induced myopathy include ptosis and ophthalmoparesis, with AChR antibodies detected in up to 40% of patients[10,11,19,20] and antistriational antibodies observed in up to 50% of patients.[9] These overlapping features pose a risk of misdiagnosis. A recent comprehensive global pharmacovigilance study analysing a decade of irAE reports (n = 50,347) revealed that ICI-induced myotoxicity (6.6%), including myositis, myocarditis, and MG-like syndromes, exhibited the greatest irAE overlap (up to 30% co-occurrence vs <3% for other irAEs).[21] However, VigiBase-derived irAE data lack detailed clinical information. Other reviews synthesizing published

cases and cohort studies suggest that while ICI-myopathy/MG overlap exists, its prevalence may be lower than previously assumed. In some ICI myopathy patients, AChR antibodies may represent an epiphenomenon of bystander autoimmunity rather than true MG pathophysiology.[1] Therefore, for ICI myopathy patients with AChR antibodies, comprehensive clinical evaluation and electrophysiological testing remain essential to confirm the diagnosis and guide management.

Previous studies have reported that NCSs in patients with ICI myopathy are typically normal, whereas nEMG often reveals abnormalities, including short-duration, low-amplitude polyphasic motor unit potentials with early recruitment, consistent with a myopathic process, frequently accompanied by fibrillation potentials. RNS and single-fibre electromyography (SFEMG) may detect overlapping neuromuscular transmission defects in some patients.[5,11,13,22] We found that patients with poor muscle strength (MRC grade ≤4) or respiratory muscle involvement presented more pronounced nEMG abnormalities. One patient in our cohort with normal nEMG findings presented limb muscle strength graded as MRC grade 5−, likely attributed to multifocal lesions in ICI myopathy. The absence of abnormalities on nEMG may reflect limited muscle sampling, which failed to detect focal pathological changes due to the patchy distribution of myopathic involvement. These findings underscore the importance of multisite nEMG evaluation—including paraspinal and sternocleidomastoid muscles—even in patients with relatively preserved limb strength to identify subclinical evidence of ICI-induced myopathy.

One of our patients with moderately to poorly differentiated gastric cancer underwent RNS testing during follow-up six months post-onset, revealing a low-frequency decrement (3 Hz) in the facial nerve and a high-frequency increment (20 Hz) in the ulnar nerve. Clinical features included ptosis, respiratory muscle weakness, nonfluctuating symptoms, a negative neostigmine test, and the detection of anti-AChR antibodies. NCSs revealed no electrophysiological hallmarks of Lambert-Eaton syndrome. The patient died from gastrointestinal haemorrhage secondary to metastatic disease one year after follow-up.

Systematic evaluations of imaging abnormalities in large cohorts of ICI-induced myopathy patients remain limited. A study of 24 patients with ICI myopathy reported imaging abnormalities in 11 of 20 patients who underwent muscle MRI and PET scans, characterized by T2 hyperintensity with or without gadolinium enhancement on MRI and increased FDG uptake on PET. The paraspinal and masticatory muscles were most frequently involved, with nearly 50% of patients exhibiting paraspinal muscle abnormalities on imaging despite only a subset demonstrating clinical neck extensor weakness. The median time from symptom onset to imaging was 7 days (range: 1–39 days).[11]

One-third of patients with ICI myopathy may develop concurrent myocarditis, detectable via ECG and echocardiography. Prior studies recommend considering myocarditis if any of the following ECG abnormalities are observed: new PR interval prolongation, atrioventricular block, ventricular arrhythmias, frequent ventricular premature complexes, ST-segment depression, or diffuse T-wave inversion, after alternative causes such as acute coronary syndrome are excluded.[21] All 16 patients in our cohort presented with newly elevated cardiac troponin levels. Among them, three underwent cardiac magnetic resonance imaging, which revealed LGE. The remaining patients presented with clinical symptoms, myopathy (as another immune-related adverse event), and most had ventricular arrhythmias. According to the 2022 ESC Cardio-Oncology Guidelines[8] diagnostic criteria for ICI myocarditis, all patients met the criteria of troponin elevation with one major criterion or two minor criteria, and were diagnosed as having either definite ICI myocarditis or probable ICI myocarditis by experienced cardiologists. However, since only three patients underwent coronary computed tomography angiography or coronary angiography to exclude ACS, we classified these patients as having ICI-associated myopathy with concurrent myocardial injury. In addition to the abnormalities noted above, we observed new-onset sinus bradycardia in 25% of the patients. The patients in our studies who died exhibited marked ECG abnormalities at presentation, including frequent polymorphic VPCs, and broad QRS complexes. Notably, these patients initially presented with only mild limb weakness at the time of admission, and one patient showed no significant elevation in CK or CK-MB levels. For such patients, heightened vigilance for sudden cardiac death is critical, and ECG remains a critical, accessible screening tool for early detection and longitudinal monitoring in this population.

Echocardiographic detection of LVEF alterations, diastolic dysfunction, new-onset regional wall motion abnormalities, or pericardial effusion may suggest a diagnosis of ICI-associated myocarditis.[23] In a cohort of 35 ICI-associated myocarditis patients described by Mahmood et al, 51% had preserved LVEF, and 38% of patients who experienced

MACEs also exhibited normal LVEF.[12] Echocardiographic findings suggest that patients with LVEF decline may face worse clinical outcomes, consistent with prior studies indicating that severe, life-threatening myocarditis syndromes often present with low LVEF at initial evaluation.[21] GLS by speckle tracking can detect subtle ventricular dysfunction earlier than conventional LVEF, identifying subclinical myocardial injury in patients with normal LVEF. A multicenter study of 101 patients with ICI myocarditis showed that GLS was also significantly reduced (15.3±2.0%) in 60% of patients with preserved LVEF.[24] In our cohort, one patient with abnormal GLS also had LGE on cardiac MRI, while LVEF remained normal.

In the management of patients with myopathy complicated by myocarditis, guidelines from the SITC and the American Society of Clinical Oncology (ASCO) for irAEs recommend classifying these patients as CTCAE grade 4, irrespective of myopathy severity. For CTCAE grade 4, the recommended regimen includes high-dose intravenous methylprednisolone (1 g/day for 5 days) combined with either IVIg (0.4 g/kg/day for 5 days) or plasma exchange, followed by high-dose oral prednisone with gradual tapering. In patients who show no improvement after 2 weeks of therapy, second-line agents such as tocilizumab, tumour necrosis factor-alpha (TNF-α) inhibitors, and rituximab may be considered. For patients with persistent symptoms beyond 4 weeks or who require maintenance therapy, immunosuppressants, including methotrexate, azathioprine, and mycophenolate mofetil, are potential options. In our study, all 16 patients received steroid therapy, with 13 receiving high-dose methylprednisolone pulse therapy (500–1000 mg/day). Intravenous immunoglobulin (IVIg) was administered to 8 patients (50.0%), and 1 patient received adjunctive plasma exchange. Clinical improvement occurred at a median of 11.5 days (range: 1–40) post-steroid initiation, whereas creatine kinase (CK) normalization was achieved at a median of 5 days (range: 2–35), consistent with prior studies reporting a median time of 8 days (range: 1–35) from the initiation of immunosuppressive therapy to CK normalization.[11] No consensus exists regarding the optimal steroid duration or tapering protocols for ICI-associated myocarditis. The ASCO clinical practice guidelines for ICI-related adverse events recommend a minimum of 4–6 weeks of steroid tapering—a shorter course than viral myocarditis management, where steroid therapy typically extends for 3 months to 1 year.[25]

One patient in our cohort, who had the highest CK (7116 U/L), received plasmapheresis. Despite respiratory and myocardial involvement, this patient improved and was discharged after treatment with methylprednisolone pulse, IVIg, plasmapheresis, and mechanical ventilation. In contrast, neither of the two patients who died received plasmapheresis. High-dose corticosteroids remain the cornerstone of initial myopathy management. Severe weakness or myocarditis may warrant prompt immunosuppression or plasmapheresis, although the efficacy of these strategies lacks robust validation.[26] A case report described two ICI myopathy patients who demonstrated rapid strength recovery with combined steroid and plasmapheresis therapy, suggesting that early plasmapheresis in severe neuromuscular injury may reduce the corticosteroid burden and accelerate functional improvement. While plasmapheresis is not the first-line treatment for myositis, its potential utility in ICI myopathy may stem from the clearance of pathogenic antibodies hypothesized to drive disease, as hypothesized by researchers.[27] The ASCO clinical practice guidelines for ICI-related adverse events endorse plasmapheresis as a consideration based on steroid response. Given the risk of early mortality due to malignant arrhythmias, early identification of high-risk patients and timely plasmapheresis initiation may represent a viable therapeutic strategy.

A pharmacovigilance analysis using the WHO VigiBase database reported a 22.3% mortality rate among 345 ICI myopathy patients over an 11-year period, with 51.3% mortality observed in the subset (11.3%) presenting with concurrent myocarditis.[16] These findings underscore the elevated mortality risk associated with myocarditis in large-scale studies. Our data further indicate that fatal outcomes may occur as early as one week post-treatment initiation, even during periods of decreased CK and CK-MB levels. Current guidelines recommend permanent discontinuation of ICIs in patients with CTCAE grade 4 or higher adverse events,[28] including cases of mild myocarditis. Among patients with grade 2 or higher ICI myopathy who survive the acute phase and discontinue therapy, long-term follow-up has revealed that cancer progression and cancer-related mortality are major contributors to overall death rates (8–56%).[5,10,11,13] In our cohort one patient who survived the acute phase succumbed to metastatic disease one year later. The following critical questions remain unresolved: whether permanent ICI cessation is mandatory for all patients with myocarditis, the feasibility of switching to alternative ICI types, and the potential for ICI rechallenge under rigorous biomarker monitoring and concomitant steroid therapy. These issues necessitate validation through large-scale randomized controlled trials (RCTs) to optimize risk-benefit strategies in this high-risk population.

To our knowledge, cohort studies specifically examining ICI-associated myopathy remain scarce, and our study represents one of the few efforts to characterize this entity. However, several limitations should be acknowledged. First, this was a single-center retrospective study, relying on data extracted from medical records that were not originally collected for research purposes. Consequently, missing data and incomplete documentation were inevitable, which may have introduced information bias and affected the accuracy of our analyses. Second, the small sample size (n=16) limited statistical power, precluding multivariable adjustment or meaningful subgroup analyses. Therefore, the observed differences should be interpreted with caution. Third, diagnostic work-up was not standardized across patients: only a minority underwent cardiac MRI, coronary CTA, or coronary angiography, and GLS measurements were available in a subset. This inconsistency may have led to underdiagnosis or diagnostic uncertainty. Fourth, corticosteroid regimens, including initial doses and tapering schedules, were decided by individual clinicians without a predefined protocol, introducing heterogeneity in management that could have influenced clinical trajectories and outcomes. Fifth, our diagnosis of myocardial injury relied primarily on cardiac troponin elevation, without histopathological confirmation; we cannot entirely exclude other causes of troponin elevation. Given these inherent limitations, our findings should be viewed as hypothesis-generating. Prospective, multicenter studies with larger cohorts and standardized protocols are warranted to validate our observations and to better elucidate the clinical implications of cardiac enzyme fluctuations in this patient population.

Conclusion

ICI myopathy is a distinct immune-mediated disorder that emerges following cancer immunotherapy. It is characterized by skeletal and cardiac muscle involvement, with a hallmark clinical feature of nonfluctuating ptosis. It is particularly noteworthy that even patients presenting with mild clinical symptoms and only minor elevations in CK or cardiac enzymes should be carefully evaluated for electrocardiographic abnormalities and monitored for malignant arrhythmias. Early diagnosis, prompt intervention, and rigorous monitoring of laboratory parameters and cardiac rhythms during the acute phase are essential for improving outcomes.

Written Consent for Publication

Written informed consent for publication of data was obtained from all participants included in the study. The participants grant permission for their information being used in this publication and potentially in future editions and reprints of the work.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics Approval

All enrolled patients provided written, informed consent to be included in the study. All methods were performed in accordance with the relevant guidelines and regulations.

Consent to Participate

Informed consent was obtained from all individual participants included in the study. We are grateful to all study participants and their family.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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