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ORIGINAL RESEARCH

Neuromuscular and cardiac adverse events associated with immune checkpoint inhibitors: pooled analysis of individual cases from multiple institutions and literature

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized the management of multiple tumors, due to improved efficacy, quality of life, and safety. While most immune-related adverse events (irAEs) are mild and easily managed, in rare cases such events may be life-threatening, especially those affecting the neuromuscular and cardiac system. The management of neuromuscular/cardiac irAEs is not clear due to the lack of consistent data. Therefore, we carried out a pooled analysis of collected cases from selected Italian centers and individual data from published case reports and case series, in order to improve our understanding of these irAEs.

Patients and methods: We collected retrospective data from patients treated in six Italian centers with ICIs (programmed cell death protein 1 or programmed death-ligand 1 and/or cytotoxic T-lymphocyte antigen 4 inhibitor) for any solid tumor who experienced neuromuscular and/or cardiovascular toxicity. Then, we carried out a search of case reports and series of neuromuscular/cardiac irAEs from ICIs with any solid tumor.

Results: This analysis includes cases from Italian institutions ($n = 18$) and the case reports identified in our systematic literature search ($n = 120$), for a total of 138 patients. Among these patients, 50 (36.2%) had complete resolution of their neuromuscular/cardiac irAEs, in 21 (15.2%) cases there was a clinical improvement with mild sequelae, and 53 (38.4%) patients died as a result of the irAEs. Factors significantly associated with worse outcomes were early irAE onset, within the first two cycles of ICI (Fisher $P < 0.0001$), clinical manifestation of both myositis and myocarditis when compared with patients who developed only myositis or myocarditis (chi-square $P = 0.0045$), and the development of arrhythmia (Fisher $P = 0.0070$).

Conclusions: To the best of our knowledge, this is the largest collection of individual cases of immune-related myocarditis/myositis. Early irAE onset, concurrent development of myositis and myocarditis, as well as occurrence of arrhythmias are associated with worse outcomes and should encourage an aggressive immunomodulatory treatment.

Key words: immune checkpoint inhibitors, myasthenia gravis, myositis, myocarditis, melanoma, immunotherapy

INTRODUCTION

In recent years, cancer therapy has been revolutionized by the advent of immunotherapy. Since their introduction, immune checkpoint inhibitors (ICIs) have progressively become the standard of care for many advanced and early-stage solid tumors,[1] leading to unprecedented results in terms of efficacy,[2,3] quality of life,[4] and safety.[5]

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The mechanism of action of this class of drugs [programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1) inhibitors and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors] leads to the inactivation of an immunological escape pathway used by tumor cells, reactivating the anti-neoplastic effector activity by adaptive immunity.[6]

However, such reactivation may lead to a series of adverse events of autoimmune pathogenesis, directed mainly against the endocrine glands, the skin, but also the kidneys, lungs and gastrointestinal tract, and potentially affecting any organ or tissue.[7,8] In most cases, these adverse events, also called immune-related adverse events (irAEs), are clinically easy to manage and paucisymptomatic.[7,8] However, in some rare cases irAEs may be life-threatening, especially those affecting the neuromuscular system and muscle tissue, including the myocardial tissue,[7,8] identified as myositis and myocarditis, respectively.

The onset of muscular and cardiac irAEs can be acute and lead the patient to the emergency department with acute heart failure or respiratory insufficiency constituting a serious diagnostic and therapeutic challenge. The rapid identification and management of these clinical presentations is very important not only for the emergency physicians, but also for oncologists, cardiologists, or neurologists, who can be still unfamiliar with the management of these rare serious events.[9]

To face this knowledge lag, scientific societies expressed guidelines for the management of these toxicities.[7,8,10-12] However, these guidelines are sometimes conflicting and are only based on expert opinion, due to a lack of consistent data. Therefore, we collected case reports of neuromuscular and cardiac irAEs from selected Italian centers and carried out a systematic literature search to collect case reports and case series on this topic to improve our understanding of these irAEs.

PATIENTS AND METHODS

Search strategy, study selection, and data extraction

We collected retrospective data from patients, reported by the referring physicians, treated in six Italian centers with ICIs (PD-1 or PD-L1 and/or CTLA-4 inhibitor) for any solid tumor who experienced neuromuscular and/or cardiovascular toxicity up to 4 July 2021. Approval of local Ethics Committee (Liguria, Italy) was obtained. Then, we carried out a computerized search of case reports and case series of neuromuscular and/or cardiologic toxicity from ICIs with any solid tumor using the PubMed search engine with the search string reported in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2023.100791. The search included cases published from 1 January 2010 to 4 July 2021.

Case reports and case series published in English and reporting neuromuscular and/or cardiovascular toxicity in patients receiving ICIs (PD-1 or PD-L1 inhibitors and/or CTLA-4 inhibitors) were evaluated.

The following information was extracted from each report: first author and year of publication, sex and age of patients, type of cancer, cancer treatment, previous medical conditions, clinical manifestations of the adverse event, diagnostic work-up, management, outcome of the event, and cancer objective response to the ICI.

Data were independently extracted by two investigators (A.Bou. and A.Bot.) to ensure homogeneity of collection and to rule out the effect of subjectivity in data gathering and entry. Disagreements were resolved by iteration, discussion, and consensus.

Statistical analysis

Descriptive and statistical analyses were carried out on the whole of our case series and the reports extracted from the literature. Contingency analyses were carried out by using Fisher's exact test (for multiple groups chi-square test was employed instead). Group analyses for continuous variables were carried out by using the Mann—Whitney test.

For the purpose of statistical analyses, we evaluated complete remission, partial remission, death, as well as the lack of improvement without reported death. Since our analysis was based on case reports and case series, where the final outcome of the patient might be unknown, when division in sub-groups was functional to the analysis, we associated complete and partial remissions (assuming that they can both be considered favorable outcomes). Similarly, we considered both death and complete lack of improvement as unfavorable outcomes. Notably, only few patients experienced neither death nor at least partial improvement of the irAE.

The analyses were carried out using GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, www.graphpad.com); the same software was employed for developing graphs.

RESULTS

Patient characteristics

Patients identified within Italian institutions. We identified a total of 18 patients diagnosed with solid tumors who received at least one dose of ICI at six Italian centers from January 2017 to December 2020 who experienced at least one neuromuscular or cardiac irAE.

The included patients were affected by non-small-cell lung cancer (NSCLC; $n = 5$), melanoma ($n = 11$), cutaneous squamous cell carcinoma ($n = 1$), and renal cell carcinoma ($n = 1$) and had been treated with nivolumab ($n = 8$), pembrolizumab ($n = 3$), nivolumab plus ipilimumab ($n = 3$), durvalumab ($n = 2$), cemiplimab ($n = 1$), and ipilimumab ($n = 1$). Their median age was 72 years.

Selected case reports. In our systematic literature search, 71 full-texts of case reports or case series of patients with solid tumors who manifested neuromuscular or cardiac irAEs were selected, and data from 120 patients were extracted.[13-83]

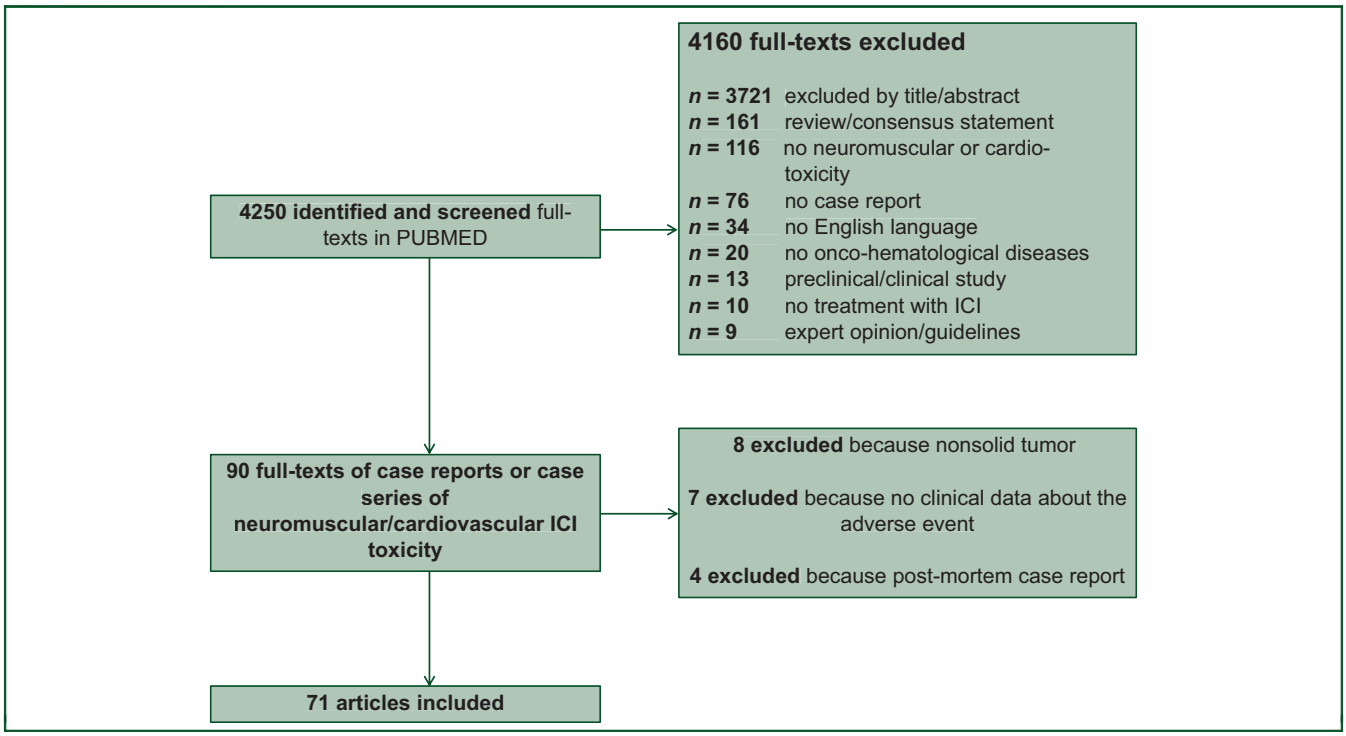

Figure 1. The PRISMA flowchart summarizing the process for the identification of the eligible studies.
ICI, immune checkpoint inhibitor.

The included patients had melanoma ($n = 56$), NSCLC ($n = 30$), renal cell carcinoma ($n = 6$), head and neck squamous cell carcinoma ($n = 4$), pancreatic cancer ($n = 4$), thymic cancer ($n = 4$), thymoma ($n = 1$), urothelial carcinoma ($n = 5$), cutaneous squamous cell carcinoma ($n = 2$), endometrial cancer ($n = 2$), hepatocellular carcinoma ($n = 2$), colorectal cancer ($n = 1$), cholangiocarcinoma ($n = 1$), mesothelioma ($n = 1$), and prostate cancer ($n = 1$). These patients received the ICIs pembrolizumab ($n = 37$), nivolumab ($n = 28$), nivolumab plus ipilimumab ($n = 25$), ipilimumab ($n = 9$), atezolizumab ($n = 4$), durvalumab plus tremelimumab ($n = 3$), atezolizumab plus cobimetinib ($n = 2$), avelumab ($n = 2$), durvalumab ($n = 4$), nivolumab plus vaccine ($n = 2$), cemiplimab ($n = 1$), chemotherapy plus pembrolizumab ($n = 1$), and sintilimab ($n = 2$). The median age was 70 years. For 110 patients, data on toxicity outcomes were reported and for 50 patients, information on the best overall response to ICI was available. The identified studies are summarized in Figure 1.

Outcome analysis

The outcome analysis of muscular/cardiac irAEs has been conducted including both cases from the Italian institutions ($n = 18$) and the case reports identified in our systematic literature search ($n = 120$), for a total of 138 patients.

Among all these patients, 50 (36.2%) had complete resolution of their neuromuscular/cardiac irAEs, and in 21 (15.2%) patients there was a clinical improvement with mild sequelae. A total of 53 (38.4%) patients died as a result of the neuromuscular/cardiac irAEs. In four (2.9%) patients no clinical improvements of the irAEs were observed; their cause of death was progressive disease ($n = 1$), complications and side effects of irAE treatments ($n = 1$), or not reported ($n = 2$). Finally, the toxicity outcomes of 10 (7.3%) patients were not reported. Individual patients' outcomes have been summarized in Supplementary Table S1 and Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.100791. No differences in terms of irAE outcomes were observed on the basis of sex or age (Fisher $P = 0.9999$ and Mann–Whitney $P = 0.3792$, respectively, Supplementary Table S2, Figures S2 and S3, available at https://doi.org/10.1016/j.esmoop.2023.100791).

No significant difference in the occurrence or outcome of cardiac/muscular irAEs was observed in patients with history of cardiovascular, respiratory, autoimmune, endocrine, or metabolic diseases. The relevant findings involving medical history and cardiac/muscular irAEs outcomes are reported in Table 1 and Figure 2.

Cancer type and outcomes. Most of the included patients had melanoma ($n = 67$), of whom 62 were cutaneous, while 4 patients had uveal melanoma and 1 had mucosal melanoma. A total of 27 (40.3%) melanoma patients had complete remission of the neuromuscular/cardiac irAE, while in 12 (17.9%) patients there was a partial improvement of the event; by contrast, 25 (37.3%) patients died due to irAEs and in one case the clinical manifestation of the irAE did not improve and did not cause death. The outcomes of the irAEs experienced by two patients were not reported. Notably, in the subgroup of patients with melanoma, nine had resected disease and were under adjuvant ICI treatment. Among these patients, six (66.6%) died as a consequence of the irAEs.

Table 1. Patients' outcomes based on history of pre-existing cardiovascular disease, endocrine/metabolic disease, chronic respiratory disease (asthma or chronic obstructive pulmonary disease), or autoimmune disease before treatment with immune checkpoint blockade

	N	Complete remission, *n*	Partial remission, *n*	Neither improvement nor death, *n*	Death, *n*	Not reported, *n*
Cardiovascular disease	60	18	12	1	29	0
No cardiovascular disease	41	21	6	3	11	0
Cardiovascular disease history not reported	37	11	3	0	13	10
Endocrine/metabolic disease	38	15	10	1	12	0
No endocrine/metabolic disease	62	24	7	3	28	0
Endocrine/metabolic disease history not reported	38	11	4	0	13	10
Chronic respiratory disease	10	4	1	1	4	0
No chronic respiratory disease	87	34	15	3	35	0
Chronic respiratory disease history not reported	41	12	5	0	14	10
Autoimmune disease	7	5	2	0	0	0
No autoimmune disease	93	35	14	4	40	0
Autoimmune disease history not reported	38	10	5	0	13	10

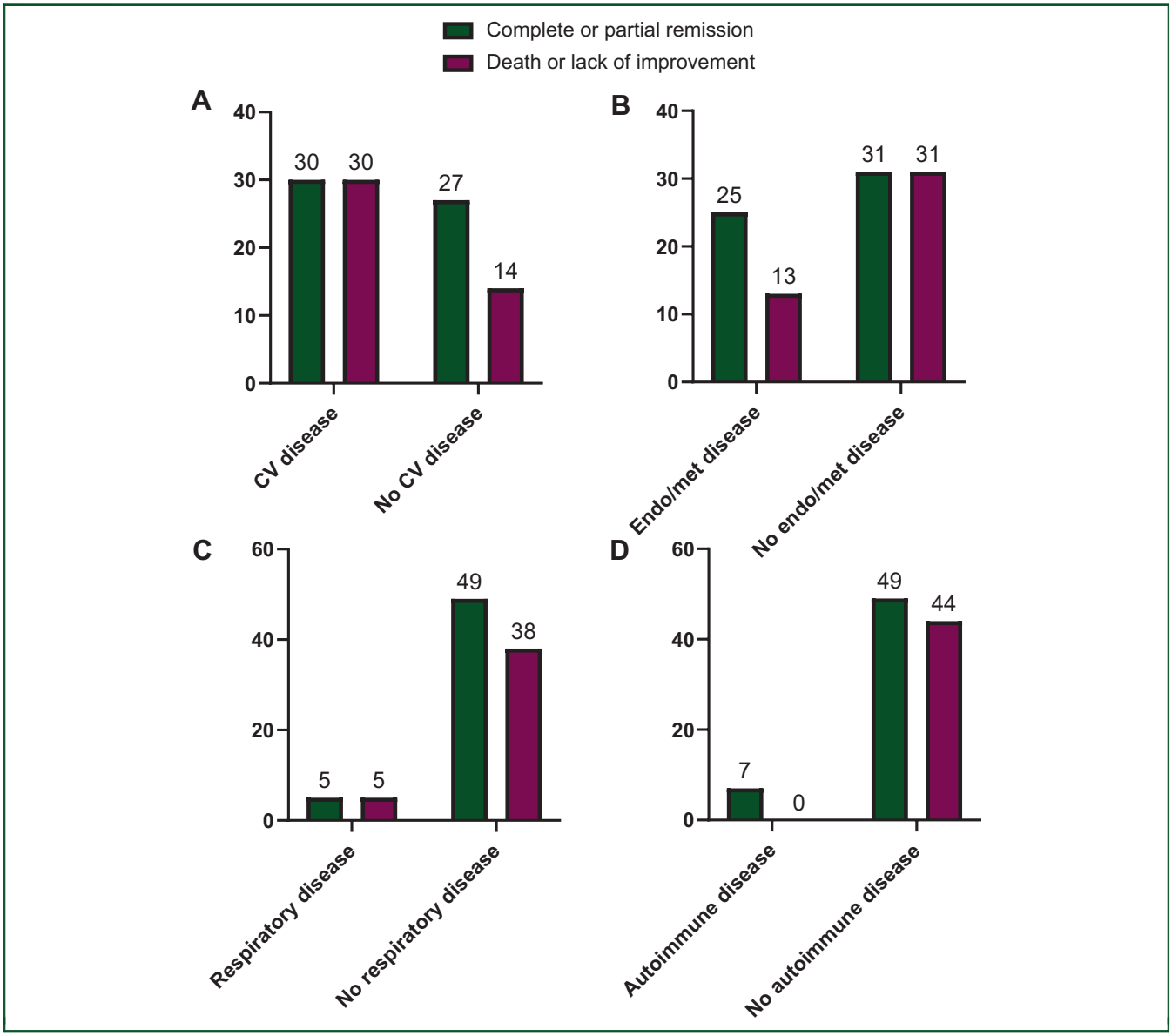

Figure 2. Outcomes of cardiac/muscular irAEs based on: (A) cardiovascular (CV) disease history (Fisher $P = 0.1529$), (B) endocrine or metabolic (endo/met) disease history (Fisher $P = 0.1487$), (C) respiratory disease history (Fisher $P = 0.7477$), and (D) autoimmune disease history (Fisher $P = 0.0169$).
irAEs, immune-related adverse events.

Table 2. Outcomes of the cardiac/muscular irAEs according to primary tumor

	N	Complete remission, *n*	Partial remission, *n*	Neither improvement nor death, *n*	Death, *n*	Not reported, *n*
Melanoma (four uveal, one mucosal)	67	27	12	1	25	2
NSCLC	35	10	5	3	15	2
RCC	7	2	1	0	4	0
HNSCC	4	1	0	0	2	1
Cholangiocarcinoma	1	0	0	0	0	1
CRC	1	0	1	0	0	0
CSCC	3	0	0	0	3	0
Endometrial cancer	2	1	1	0	0	0
HCC	2	2	0	0	0	0
Mesothelioma	1	0	0	0	1	0
Pancreatic cancer	4	1	1	0	0	2
Prostate cancer	1	1	0	0	0	0
Thymoma	1	1	0	0	0	0
Thymic cancer	4	1	0	0	2	1
Urothelial cancer	5	3	0	0	1	1
Total	138	50	21	4	53	10

CRC, colorectal carcinoma; CSCC, cutaneous squamous cell carcinoma; HCC, hepatocellular carcinoma; HNSCC, head-neck squamous cell carcinoma; irAEs, immune-related adverse events; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma.

The second most frequent cancer type was NSCLC. Among the 35 patients with NSCLC, 10 (28.6%) totally recovered, 5 (14.3%) had improvement of the irAE, 15 (42.9%) died, and 3 (8.6%) did not improve or die according to the report; data regarding the irAEs outcomes were not reported for 2 patients with NSCLC.

With regard to patients with other malignancies ($n = 36$), 13 (36.1%) had complete remission, 4 (11.1%) had partial improvement, 13 (36.1%) died, and none had persisting event with no improvement, while outcomes of 6 patients were not reported. Globally, no difference in terms of outcomes was observed based on primary tumor (chi-square $P = 0.3750$), as reported in Table 2 and Figure 3.

Immunotherapy regimen and outcomes. We also investigated the neuromuscular/cardiac events outcomes in patients receiving single-agent ICI (PD-1/PD-L1 or CTLA-4 inhibitor) and in patients receiving a combination of ICI (PD-1/PD-L1 inhibitor plus CTLA-4 inhibitor). Among a total of 102 patients treated with single-agent ICI, data on the adverse events outcomes were reported in 92 cases. Among them, 37 (40.2%) patients totally recovered from the irAEs, 15 (16.3%) had a partial resolution, 4 (4.4%) did not have any improvement, and 36 (39.1%) died from the adverse events.

In the ICI combination group ($n = 36$), a total of 13 (36.1%) patients had complete resolution of the adverse events, while 6 (16.7%) had a partial resolution and 17 (47.2%) died as a result of the adverse events. When the outcomes of cardiac/muscular irAEs of single-agent ICI and dual ICIs were compared, no significant difference was observed (Fisher $P = 0.6796$). Data are summarized in Table 3 and Figure 3.

Clinical manifestation of irAEs and outcomes. Among 132 patients for whom the number of cycles before the onset of irAE was reported, in 96 (72.7%) of them the muscular and/or cardiac adverse event occurred within the first two cycles of therapy. In this subgroup of patients, data on irAEs outcome were reported in 89 patients: muscular/cardiac adverse events were lethal in 48 (53.9%), while 30 (33.7%) and 9 (10.1%) patients had complete and partial resolution of irAEs manifestations, respectively. In the group of patients whose toxicity onset was observed after the second cycle of ICI ($n = 36$), data on outcome of adverse events were reported in 33 patients, of whom 17 (51.5%) totally recovered, 11 (33.3%) partially recovered, and 3 (9.1%) died due to the adverse events. When early onset (within the first two cycles) and late onset (after two cycles) were compared, a statistically significant difference in terms of outcome was detected (Fisher $P < 0.0001$), as earlier onset of the irAE was associated with worse outcomes (Figure 3; Table 4).

Among the patients who manifested only myocarditis ($n = 49$), 18 (36.7%) patients had complete resolution of the adverse event, 10 (20.4%) patients achieved partial clinical improvement of the event, and 21 (42.8%) patients died. With regard to patients who had only myositis ($n = 46$), the outcomes were known for 40 patients. Among these, 21 (52.5%) patients had complete resolution of myositis, 8 (20.0%) patients had partial clinical improvement, 1 (2.5%) patient did not achieve any improvement, and 10 (25.0%) patients died due to myositis.

With regard to patients who experienced both myositis and myocarditis and whose outcome was known ($n = 39$ out of 43), the following data were reported: 11 (28.2%) patients had complete recovery from the adverse events, 3 (7.7%) patients had a partial clinical improvement of the event, 3 (7.7%) patients did not have any clinical improvement but did not die, while a total of 22 (56.4%) patients died. The patients who developed both myositis and myocarditis experienced significantly worse outcomes compared to patients who developed only myositis or myocarditis (chi-square $P = 0.0045$), as reported in Table 4 and Figure 3.

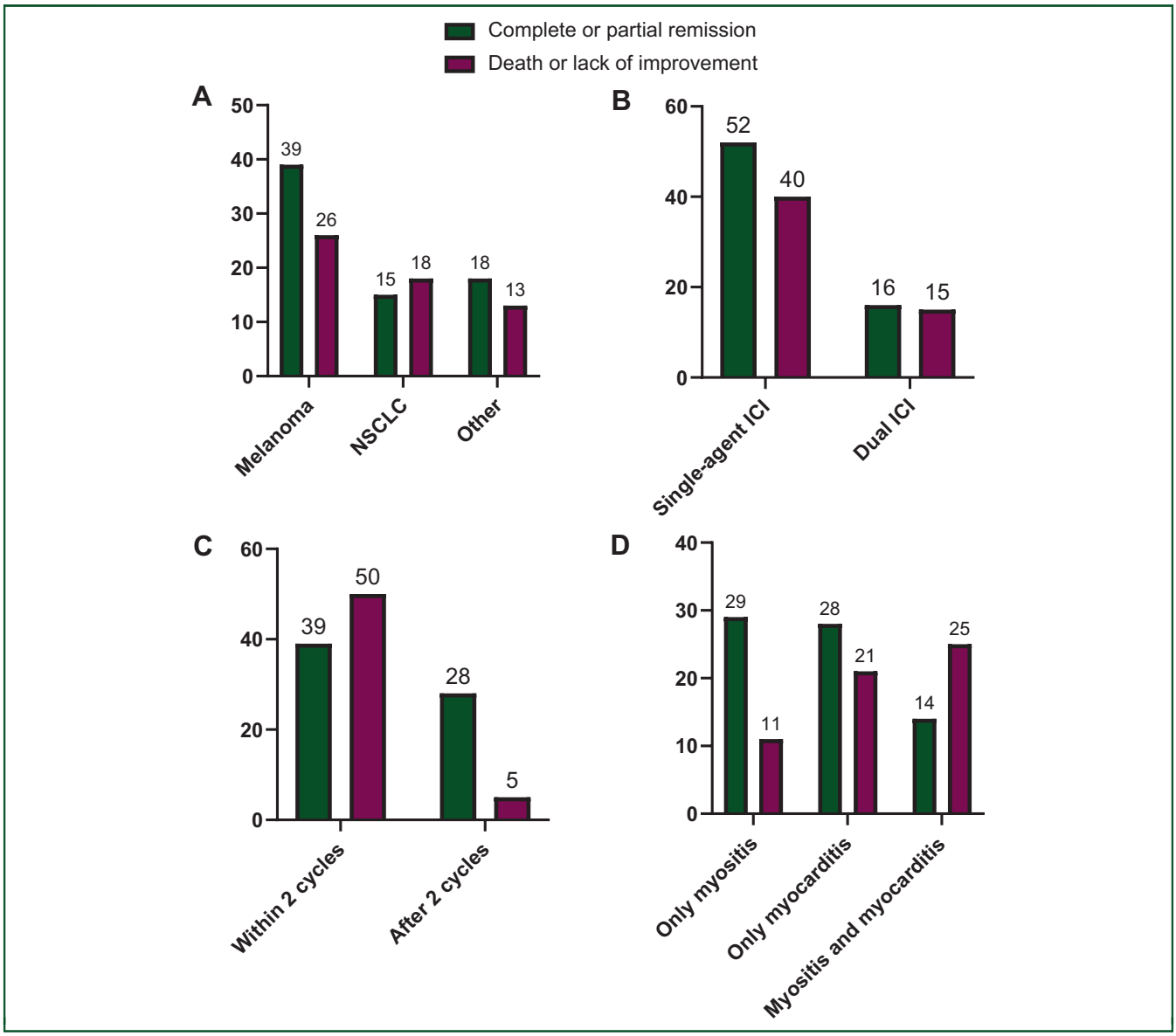

Figure 3. Outcomes of cardiac/muscular irAEs based on: (A) primary tumor (chi-square $P = 0.3750$), (B) use of single-agent ICI (anti-PD-1 or PD-L1) or dual ICIs (anti-PD-1/PD-L1 plus anti-CTLA-4) (Fisher $P = 0.6796$), (C) time of onset of the muscular/cardiac irAE (Fisher $P < 0.0001$), and (D) clinical manifestations of the muscular/cardiac irAE (chi-square $P = 0.0045$).

CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

When myositis was present and the involved muscular districts were reported ($n = 85$), they predominantly included limb muscles ($n = 55$), axial muscles ($n = 45$), oculomotor muscles ($n = 36$), diaphragm ($n = 23$), and muscles of the ENT (ear, nose, and throat) district ($n = 27$), as reported in Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2023.100791. Notably, each patient could have more involved muscular districts at

Table 3. Outcomes of the cardiac/muscular irAEs according to immunotherapy regimen

	N	Complete remission, *n*	Partial remission, *n*	Neither improvement nor death, *n*	Death, *n*	Not reported, *n*
Monotherapy (PD-1/PD-L1or CTLA-4 inhibitor)	102	37	15	4	36	10
Combination (PD-1/PD-L1 + CTLA-4 inhibitor)	31	10	6	0	15	0
Combination (PD-1 inhibitor + chemotherapy)	1	0	0	0	1	0
Combination (PD-1 inhibitor + vaccine)	2	1	0	0	1	0
Combination (PD-L1 inhibitor + MEK inhibitor)	2	2	0	0	0	0

CTLA-4, cytotoxic T-lymphocyte antigen 4; irAEs, immune-related adverse events; MEK, mitogen-activated protein kinase kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Table 4. Outcomes of the cardiac/muscular irAEs according to time of onset (within two cycles or after two cycles), clinical manifestation (only myositis, only myocarditis, or both), and instrumental findings

	N	Complete remission, *n*	Partial remission, *n*	Neither improvement nor death, *n*	Death, *n*	Not reported, *n*
≤2 cycles	96	30	9	2	48	7
>2 cycles	36	17	11	2	3	3
Only myositis	46	21	8	1	10	6
Only myocarditis	49	18	10	0	21	0
Both myositis and myocarditis	43	11	3	3	22	4
LVEF ≤45%	22[a]	6	6	1	9	0
LVEF> 45%	54[a]	20	9	2	22	1
Arrhythmia at ECG	47[b]	11	6	2	27	1
No arrhythmia at ECG	37[b]	16	8	1	10	2
Ischemic signs at ECG	19[b]	8	2	0	9	0
No ischemic signs at ECG	65[b]	19	9	3	27	7

ECG, electrocardiogram; irAEs, immune-related adverse events; LVEF, left ventricular ejection fraction.
[a]Only 76 patients had data on echocardiographic assessment of LVEF.
[b]Only 84 patients had data on ECG.

once. Due to the diagnostic heterogeneity in the reported cases, and the underreporting of acetylcholine receptor auto-antibodies values, no cases of 'myasthenia gravis' were classified in our analysis.

Laboratory findings and outcomes. In a total of 93 patients, the creatine kinase enzyme (CK) blood levels have been assessed at the onset of the irAE. In most cases, the peak value was reported, while in some cases the value was not reported and CK was defined as 'elevated', 'normal', or above various cut-off values. A total of 78 (83.9%) patients had increased CK (considering the upper normal limit of 200 U/l). The median CK value was 1900 U/l (grade 3 according to the Common Terminology Criteria for Adverse Events v.5). No significant difference in terms of outcomes was observed on the basis of peak CK value (Mann–Whitney $P = 0.2995$).

With regard to troponin, only data for 54 patients were available. Among these, 10 researchers reported the use of troponin T, while for other 33 cases the use of troponin I was reported and in 11 cases the specific troponin employed was not reported. Considering these limitations and considering an upper normal limit value of 0.04 ng/ml, most patients ($n = 48$, 88.9%) had troponin values above the upper normal limit. The median value of troponin was 2.965 ng/ml. Notably, patients with higher troponin values had numerically higher risk of unfavorable outcomes of the muscular/cardiac irAE, albeit significance was not reached (Mann–Whitney $P = 0.0830$). The irAEs outcomes based on CK and troponin values are summarized in Figure 4 and Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.100791.

Instrumental findings and outcomes. In patients with myocarditis, we analyzed the cardiovascular diagnostic work-up that was undertaken.

In 76 patients who had echocardiographic assessment of left ventricular ejection fraction (LVEF) at the onset of myocarditis, 22 (28.9%) patients had LVEF ≤45% and 54 (71.1%) patients had LVEF >45%. Among patients with reduced LVEF and known outcome data, in 6 (27.3%) patients myocarditis resolved without sequelae, whereas in 9 (40.9%) cases the event led to patient's death. In a total of six (27.3%) cases of myocarditis improved with sequelae and in one (4.5%) patient, the adverse event did not improve and did not lead to patient's death, with no additional information on patient's outcome. In contrast, in patients with preserved LVEF and known outcome data ($n = 53$), 20 (37.8%) had complete resolution of the adverse event and in 9 (16.9%) patients there was partial remission of the adverse event, whereas in 2 cases (3.8%) there was no improvement nor worsening of the event, and in 22 (41.5%) the adverse event led to patient's death. When patients' outcomes were compared on the basis of LVEF (cut-off value: 45%), no significant differences were observed (Fisher $P = 0.9999$).

An electrocardiogram (ECG) was carried out in 84 patients. No arrhythmia was found in 37 (44.0%) patients, whereas new-onset cardiac conduction disturbances were found in 47 (56.0%) patients (including atrioventricular blocks, grade 3 atrioventricular block in 17 patients). The irAE outcomes were not reported in one case with arrhythmia at ECG and two cases with no arrhythmia. Among patients with new-onset arrhythmia, toxicity completely resolved in 11 (23.9%) and resulted in death in 27 (58.8%) patients, while 6 (13.0%) patients achieved a clinical improvement of the adverse event and in 2 (4.3%) patients there was no improvement of the myocarditis. In contrast, among patients with no arrhythmia, where reported, myocarditis completely resolved in 16 (45.7%), whereas it led to death in 10 (28.6%) patients or improved with some sequelae in 8 (22.9%) patients. When we compared the outcomes of patients with or without arrhythmia, we identified a statistically significant difference favoring patients without arrhythmia (Fisher $P = 0.0070$).

Ischemic signs were detected in 19 patients, whereas no ischemic signs were detected in 65 patients. In the group of patients without ischemic signs on ECG, 19 (32.8%) patients had complete remission from myocarditis, 9 (15.4%) patients had clinical improvement, 3 (5.2%) patients did not have any clinical improvement and 27 (46.6%) patients died

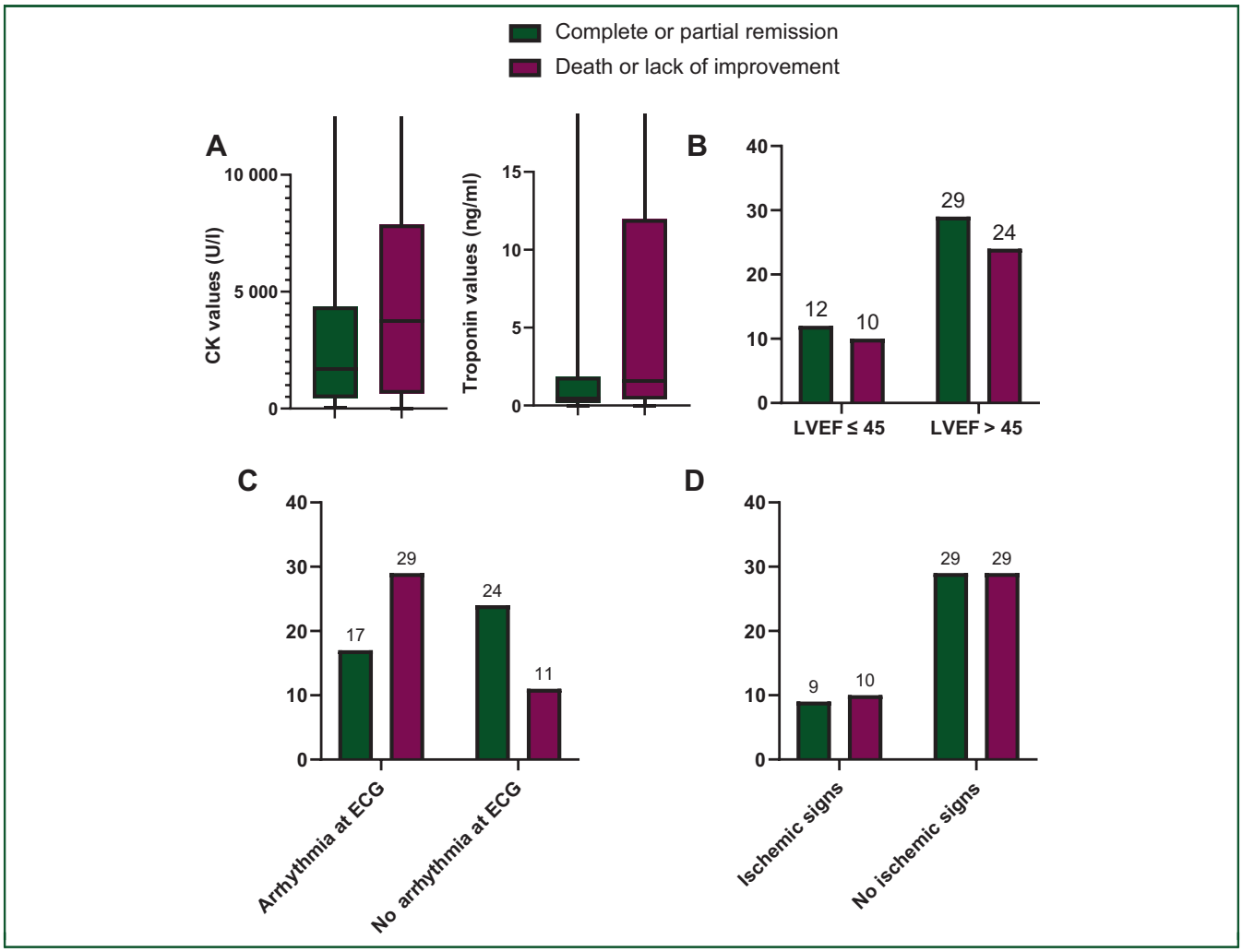

Figure 4. Outcomes of cardiac/muscular irAEs based on: (A) creatine kinase (CK) values (Mann–Whitney $P = 0.2995$) and troponin values (Mann–Whitney $P = 0.0830$), (B) left ventricular ejection fraction (LVEF) (chi-square $P = 0.9999$), (C) finding of arrhythmia at electrocardiogram (ECG) (chi-square $P = 0.0070$), and (D) ischemic signs at ECG (chi-square $P = 0.9999$). The outliers of the box-and-whisker plot are above the maximum value of the 'y' axis in order to make the plot more easily readable.
irAEs, immune-related adverse events.

due to the adverse events (data were not reported for 7 patients). In this subgroup, a coronary study was carried out in 11 patients; at coronarography, coronary abnormalities were detected in the case of one single patient who had a history of coronary artery disease. Among 19 patients with ischemic signs on ECG, 8 (42.1%) had complete remission, 2 (10.5%) had clinical improvement, and 9 (47.4%) died due to myocarditis. In this subgroup, coronary angiography was carried out in 11 patients, all without alterations. When patients with and without ischemic signs at ECG were compared in terms of outcomes, no significant differences were observed (Fisher $P = 0.9999$). The irAEs outcomes based on ECG and echocardiography are summarized in Table 4 and Figure 4.

With regard to cardiac magnetic resonance, we identified 25 patients who underwent the exam, of which only 12 had late gadolinium enhancement. Among the patients for whom magnetic resonance data were available ($n = 15$), only in 5 (33.3%) cases with mild alterations in terms of left ventricular posterior wall thickening were reported. No significant differences were observed on the basis of magnetic resonance findings (Fisher $P = 0.9999$), albeit the number of assessable patients was extremely limited. Data on cardiac magnetic resonance are reported in Supplementary Table S4 and Figure S5, available at https://doi.org/10.1016/j.esmoop.2023.100791.

Finally, electromyography data were available for 35 patients; notably, almost all the patients (31 out of 35, 88.6%) had some degree of conduction alteration. Due to the extremely limited number of patients with negative electromyography, no comparison was carried out.

Treatment of the immune-related adverse events and outcomes. A total of 106 patients were reported to have received corticosteroid therapy; of these, 59 patients received exclusive steroidal therapy, without other immunosuppressive agents. Among those who received exclusive steroid therapy, 24 (40.7%) had complete resolution from irAE, 13 (22.0%) clinically improved without reaching complete resolution of the irAEs, whereas 20 (33.9%) died.

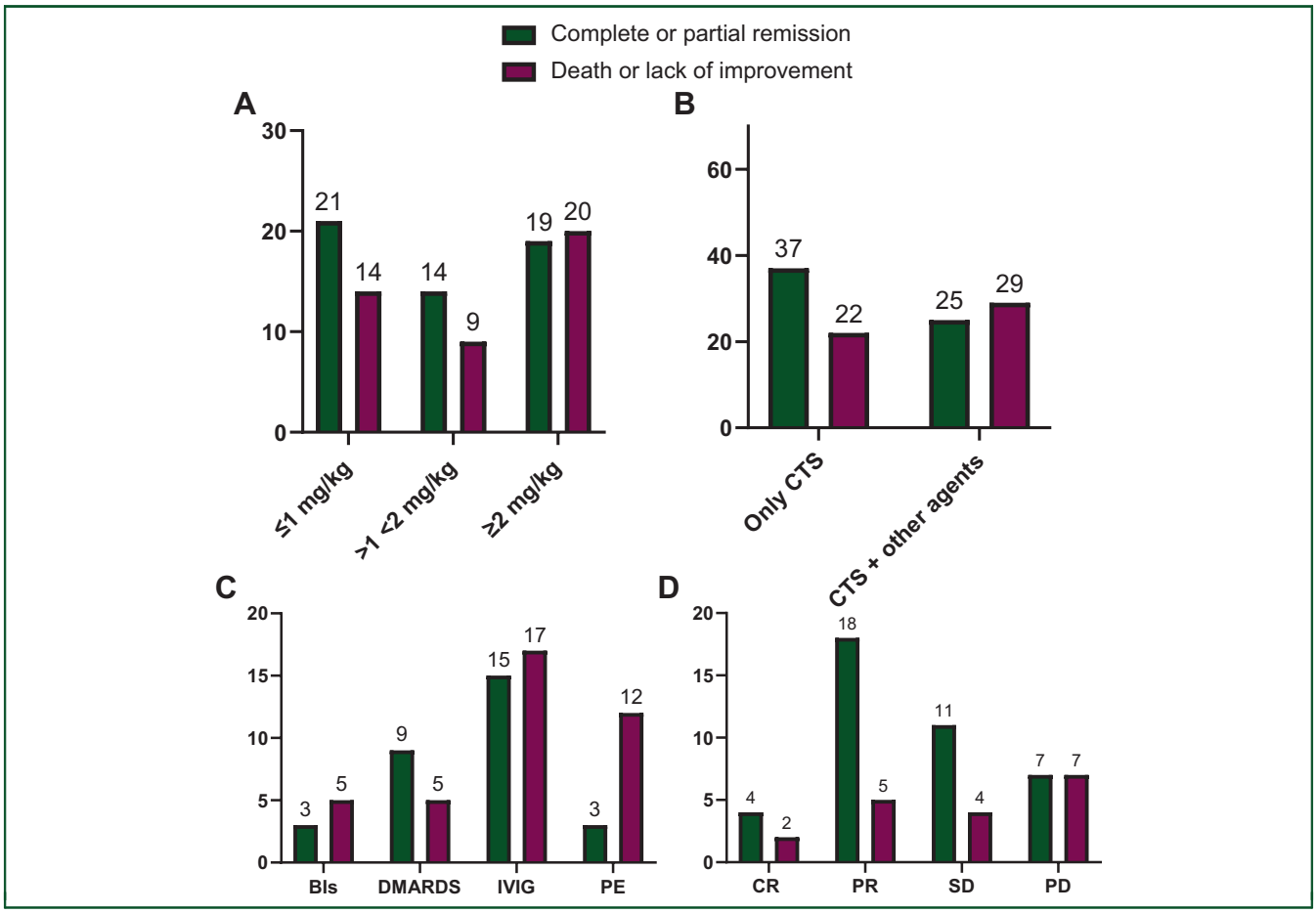

Figure 5. Outcomes of cardiac/muscular irAEs based on: (A) the maximum daily reported dose of CTS (prednisone or equivalent dose) (chi-square $P = 0.5269$), (B) exclusive use of CTS versus association with other agents (Fisher $P = 0.0913$), (C) use of specific immunomodulatory agents (chi-square $P = 0.1070$), and (D) best tumor response (chi-square $P = 0.3300$).
BI, biologic immunosuppressant; CR, complete response; CTS, corticosteroids; DMARD, disease-modifying antirheumatic drug; IVIG, intravenous immunoglobulins; irAEs, immune-related adverse events; PD, progressive disease; PE, plasma exchange; PR, partial response; SD, stable disease.

We also analyzed the corticosteroid dosage used (where reported): in a total of 35 patients, a corticosteroid dosage of no >1 mg/kg daily was administered. Of these, 13 (37.1%) had complete remission from symptoms, 8 (22.9%) had clinical improvement without reaching complete remission, and 12 (34.3%) died due to the adverse event. In a total of 23 patients, a maximum daily dose of corticosteroid between 1 and 2 mg/kg was used. Of these, toxicity completely resolved in 9 (39.1%) patients, improved without complete remission in 5 (21.7%) patients, and led to death in 8 (34.8%) patients. In contrast, a total of 39 patients received daily doses of corticosteroid ≥2 mg/kg, with complete remission in 14 (35.9%) patients, partial clinical improvement in 5 (12.8%), and death in 20 (51.3%) cases. No differences in outcomes were observed on the basis of maximum daily dose of corticosteroid (chi-square $P = 0.5269$). Notably, when we compared the outcomes of patients treated exclusively with corticosteroids or corticosteroids followed by or associated with other agents, we observed a non-significant difference in outcome favoring patients who received corticosteroids alone (Fisher $P = 0.0913$).

With specific regard to other immunosuppressive agents, a total of 14 patients received a disease-modifying antirheumatic drug (DMARD), with 8 (57.1%) of the patients in complete remission from the adverse event and 5 (35.7%) of the patients deceased. Among the eight patients to whom a biologic immunosuppressant drug was administered, one (12.5%) patient had a complete remission, two (25.0%) had a partial remission, and five (62.5%) patients died. A total of 32 patients also received intravenous immunoglobulin (IVIG), with 12 (37.5%) of the patients in complete remission, and a 50% ($n = 16$) death rate. A total of 16 patients also received plasma exchange, with only 2 (12.5%) patients in complete remission from toxicity and 11 (68.8%) deceased patients. When the collective outcomes were based on the employed agents, no significant difference was observed (chi-square $P = 0.1070$), albeit DMARDs achieved a notable benefit. Outcomes of the irAEs based on immunomodulatory treatments were summarized in Figure 5 and Table 5.

Cancer best overall response and outcomes. Of a total of 58 patients whose toxicity outcome was known and objective response to ICI was assessed on the *in vivo* or post-mortem context (based on autoptic findings), 15 (25.9%) had progressive disease, 15 (25.9%) had stable

Table 5. Outcomes of the cardiac/muscular irAEs according to immunosuppressive treatments and according to best overall tumor response among patients with available treatment and tumor response data based on RECIST

	N	Complete remission, *n*	Partial remission, *n*	Neither improvement nor death, *n*	Death, *n*	Not reported, *n*
CTS treatment plus other agents	55	19	6	2	27	1
Only CTS	59	24	13	2	20	0
CTS $\leq$ 1 mg/kg	35	13	8	2	12	0
CTS >1 and <2 mg/kg	23	9	5	1	8	0
CTS $\geq$ 2 mg/kg	39	14	5	0	20	0
Biologic immunosuppressant	8	1	2	0	5	0
DMARDS	14	8	1	0	5	0
IVIG	32	12	3	1	16	0
Plasma exchange	16	2	1	1	11	1
Complete response	6	3	1	0	2	0
Partial response	23	11	7	0	5	0
Stable disease	15	8	3	0	4	0
Progressive disease	15	6	1	1	6	1

CTS, corticosteroids; DMARD, disease-modifying antirheumatic drug; irAEs, immune-related adverse events; IVIG, intravenous immunoglobulin.

disease, 23 (39.7%) had a partial response, and in 6 (10.3%) a complete response was observed (these were 3 patients with NSCLC, 2 patients with melanoma, and 1 patient with thymic cancer).

Among patients who had progressive disease, where data on the irAEs outcomes were reported ($n = 14$), a total of six (42.9%) patients had complete remission of the adverse event, one (7.1%) patient had clinical improvement without complete remission, one (7.1%) patient had no clinical improvement, and six (42.9%) patients died due to the irAEs. Among patients who had stable disease, partial, or complete response ($n = 44$), a total of 22 (50.0%) patients had complete remission of the irAEs, 11 (25.0%) had clinical improvement without complete remission, and 11 (25.0%) died due to neuromuscular/cardiac event. No differences in terms of irAEs outcomes were observed on the basis of tumor response (chi-square $P = 0.3300$), albeit patients with controlled disease (response or stable disease) achieved numerically better outcomes compared with patients experiencing disease progression as best response. Outcomes of the irAEs based on tumor response to immunotherapy are summarized in Figure 5 and Table 5.

Additional analyses have been carried out on patients' medical history, biopsy findings, and autoimmunity markers in Supplementary Analyses a, b, and c, in Supplementary Table S5, and in Supplementary Figure S6, available at https://doi.org/10.1016/j.esmoop.2023.100791.

DISCUSSION

Immunotherapy is acknowledged as a generally safe and well-tolerated approach in cancer treatment, especially when employed as a single agent across various solid tumors.[84] Most irAEs are mild or moderate at their onset, and their management is relatively easy due to the use of corticosteroids. Furthermore, across the recent years, physicians have developed extensive expertise in the management of irAEs, thus becoming keen on the timely detection and prompt management of such events, usually with complete remission. However, cardiomuscular irAEs, with specific reference to myocarditis and myositis, still represent an alarming and potentially life-threatening event during treatment with ICIs.[85] Indeed, these events are globally rare, as the global incidence of myocarditis is reportedly <1%, although an incidence increase is observed with dual immune checkpoint blockade compared to single-agent blockade. However, their severity has induced international guidelines to include data on epidemiology and management. Notably, while some guidelines specifically refer to myocarditis, in other cases the two events are analyzed together as they are considered part of the same spectrum of toxicity.[80-82]

In our work, we carried out a retrospective, multicentric analysis of 18 patients who had received ICIs for solid tumors and experienced myocarditis/myositis; furthermore, we collected suitable case reports of immune-related myocarditis and myositis from the literature, thus reaching a total number of 138 assessable patients. To the best of our knowledge, this is the largest collection of individual cases of myocarditis/myositis during treatment with ICIs for solid tumors. Due to the strict correlation between myocarditis and myositis, we decided to analyze the occurrence of both events.

The first observation of our study is represented by the global outcomes; considering that 53 out of 138 patients (38.4%) died, our findings confirm the severity of myocarditis/myositis. With regard to pre-existing conditions, no specific comorbidity was consistently associated with more or less favorable outcomes, with the exception of the few patients with known autoimmune disease. However, no conclusion can be drawn from this subgroup due to their extremely limited number ($n = 6$). By contrast, the clinical manifestations of the irAE were significantly associated with outcomes; more specifically, an earlier onset (within the first two cycles) and the coexistence of both myocarditis and myositis were associated with a higher risk of death. Furthermore, our analysis found no differences in the frequency of irAEs in patients treated with single-agent ICI versus dual ICIs. This may be attributed to the fact that,

currently, fewer patients are generally treated with ICI combinations (than ICI monotherapy), thus resulting in fewer reported cases.

With regard to diagnostic work-up, the American Society of Clinical Oncology Clinical Practice Guideline suggests that upon the occurrence of myocarditis-related symptoms, ECG, troponin dosing, B-natriuretic peptide (BNP) dosing, echocardiogram, and chest X-ray should be carried out, while cardiac magnetic resonance can be considered.[86] The required exams for myositis include CK, transaminases, and lactate dehydrogenase (LDH), while electromyography and auto-antibody testing are suggested. Tissue biopsy is encouraged, when feasible.[86] In our analysis, higher troponin values were numerically associated with increased risk of death, albeit the association was not statistically significant; such findings are consistent with current guidelines.[81-82] Additionally, it has been suggested that troponin dosing should be carried out at baseline, before receiving ICIs, and especially when dual blockade is employed;[86] this approach might help interpret subsequent troponin values during treatment with ICIs, since different causes of troponin increase might be present, especially among patients with lung cancer.[87]

In addition to troponin and CK, we tried to assess other circulating biomarkers, including liver transaminases and BNP; unfortunately, we were not able to collect consistent data from the various case reports, especially when we considered the peak values. With regard to autoimmunity, a relevant variety of different auto-antibodies was detected, preventing consistent assessments; furthermore, the baseline value of auto-antibodies before receiving ICIs, which might be an interesting information for screening approaches, was not consistently available.

With regard to instrumental exams, most patients were negative for ischemia at ECG or impaired ejection fraction at echocardiography, and none of these parameters influenced the toxicity outcomes, with the exception of arrhythmia at ECG, which was significantly associated with worse outcomes. It has been observed that patients treated with ICIs might experience severe cardiac/muscular irAEs without prior cardiovascular signs, potentially complicated by the development of rhythm alterations.[88] When we evaluated cardiac magnetic resonance findings among patients with myocarditis, we noticed that in most cases the exam was negative, suggesting that the exam might not be pivotal for the management of myocarditis, despite proving to be a highly specific imaging test.[89] However, we also noticed that only few patients underwent magnetic resonance, and most of them had a favorable outcome. It is possible that in many cases the magnetic resonance might have been proposed only to patients with stable or mild symptoms, eventually in order to confirm the diagnostic hypothesis of myocarditis, while patients with unfavorable outcomes might have died before undergoing magnetic resonance or the exam might have not been proposed due to a clear diagnosis with other exams. Conversely, most patients who underwent electromyography for myositis had evidence of conduction alterations, which is consistent with symptom development. Finally, a non-negligible proportion of patients underwent tissue biopsy, consistently with guidelines. In most cases, inflammatory infiltrate, mostly based on lymphoid cells, was reported. Overall, the diagnosis of immune-related myositis and myocarditis is therefore necessarily clinical and is based on: (i) correlation with ICI therapy; (ii) clinical symptoms of acute heart failure and/or arrhythmia for myocarditis and of myalgia and/or myasthenic signs for myositis and myasthenia gravis; and (iii) CK and/or troponin elevation.

Once myocarditis and/or myositis are detected, the therapeutic approach suggested by the available guidelines includes ICI interruption and immunomodulatory treatments, starting with corticosteroids. However, apart from interruption (ultimately leading to discontinuation in severe cases), the relatively scarce scientific evidence does not allow to define structured guidelines, and even the revisors state that treatment recommendations are based on anecdotal evidence and the risk of death due to the event. Indeed, most indications rely on the use of high-dose steroids, referral to a specialist such as cardiologists or neurologists, and use of 'second-line' treatments when immediate response to high-dose corticosteroids is not observed, including, among others, mycophenolate, infliximab (albeit it is contraindicated in case of moderate-severe cardiac failure), or antithymocyte globulin.[86] However, the approaches in common clinical practice may vary on the basis of expertise and readily available immunosuppressive agents.

In this case series, when patients exclusively received corticosteroids, their outcomes were numerically, albeit non-statistically, better than when corticosteroids were followed by other agents. While this finding might appear surprising at the first glance, it is easily explained by the fact that patients not responding to corticosteroids in the first place are subsequently treated with other agents. No other relevant conclusion could be drawn with regard to the effect of immunomodulatory agents on the outcomes of irAEs, mostly due to the high variability of employed therapeutic approaches and different dosing of corticosteroids over time for each individual patient. Furthermore, the analysis of the case reports did not allow a proper identification of the average duration of the steroidal treatment, and consequently it was neither possible to identify its timing nor to estimate the appropriate time to consider treatment failure.

We are aware that this analysis is characterized by several limitations. In the first place, our data have been collected from published case reports and case series; indeed, case reports are usually emblematic in their nature, and do not usually represent the normal distribution of cases among the population. Additionally, case reports from different authors lack the consistency of a systematic data collection from populations of consecutive patients, and different clinicians might have adopted different diagnostic and therapeutic approaches at the irAE onset. Finally, the outcome data of some irAEs have not been defined, as some patients achieved improvement of their irAE but not resolution, while few patients had stability of the event, without improvement or death. However, these issues reflect the limits of the data from the literature.

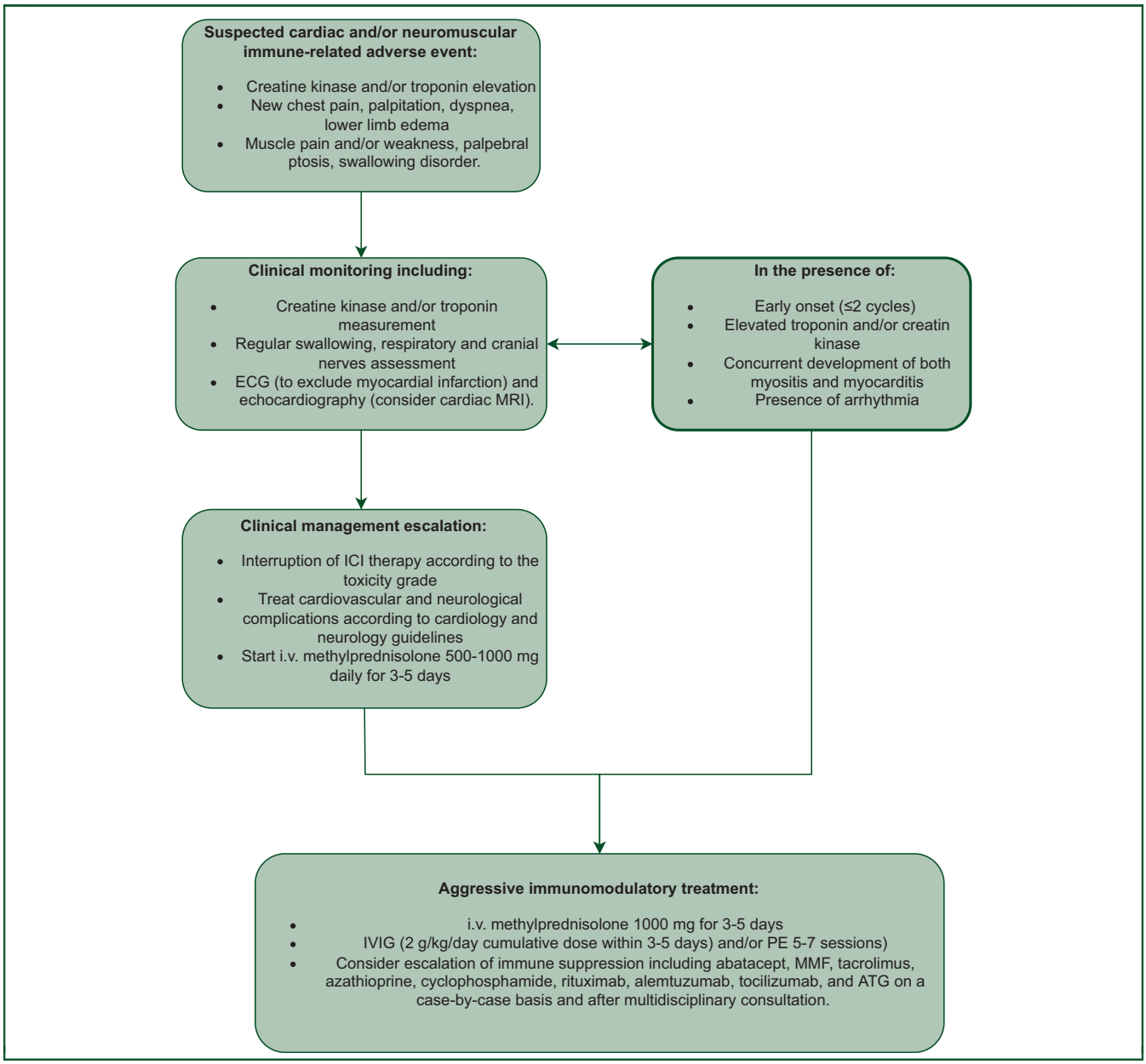

Figure 6. Suggested management of immune-related neuromuscular and/or cardiac irAEs.
irAEs, immune-related adverse events.

Theoretically, prospective multicentric studies designed to monitor the onset of irAEs among patients treated with ICIs might address many of the current questions regarding the proper management of myocarditis and myositis. However, such studies would require large numbers of enrolled patients and long follow-up time; until then, the currently available guidelines should be used. In order to provide additional information, we included an algorithm summarizing suggested indications for the management of neuromuscular and/or cardiac irAEs according to the currently available literature (Figure 6).

In conclusion, myocarditis and myositis represent rare but potentially lethal irAEs. Our data support the current management guidelines published by international scientific societies. Early irAE onset, concurrent development of both myositis and myocarditis, and occurrence of arrhythmias are associated with worse outcomes and should encourage an aggressive immunomodulatory treatment.

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DISCLOSURE

FS received honoraria for presentations or lectures from Sanofi Genzyme, Roche, BMS, Novartis, Merck, Sunpharma, MSD, Pierre Fabre, advisory boards for Novartis, Philogen, Sunpharma, MSD. GB received contracts from AstraZeneca, GSK, honoraria from Roche and Pierre Fabre, advisory boards for Pierre Fabre and Roche. FDR received honoraria from MSD, Sunpharma, Pierre Fabre, Novartis, BMS. RM received honoraria for presentations or lectures from BMS, Novartis, Ipsen, Pierre Fabre, MSD, Roche, Sanofi, AAA, advisory boards for Novartis, BMS, Ipsen, Pierre Fabre, MSD. ML received honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Knight, Takeda, advisory boards for Roche, Lilly, Novartis, AstraZeneca, MSD, Exact Sciences, Seagen, Gilead, Pfizer, and received honoraria from AstraZeneca, BMS, Boehringer-Ingelheim, MSD, Roche. All other authors have declared no conflicts of interest.

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