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ORIGINAL RESEARCH

Characteristics, Incidence, and Management of Immune Checkpoint Inhibitors Related Cardiovascular Adverse Events in Real-World Practice-A Retrospective Study in Chinese Han Population

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Purpose: This study aimed to elaborate on the incidence, clinical features, and management of immune checkpoint inhibitors (ICIs) related cardiovascular adverse events (CVAEs) in real-world practice.

Patients and Methods: We performed a retrospective chart review study on patients receiving at least one dose of ICI therapy at a Chinese tertiary hospital from March 2020 to March 2021. CVAEs were identified through clinical assessment and the Naranjo algorithm. The management and outcomes of CVAEs were monitored over a median follow-up duration of 8 months.

Results: Among the included 203 patients, 4.4% (9/203) developed CVAEs, including heart failure (n = 3), arrhythmia (n = 2), myocarditis (n = 2), and pericardial disease (n = 2), with a proportion (6/9) tending to be severe (grade 3 or grade 4). CVAEs were more common in older patients (mean age: 73.6 ± 9.2 years) and those with hypertension (p = 0.02) or heart failure (p = 0.01). Adherence to the American Society of Clinical Oncology (ASCO) guidelines for managing CVAEs was low (44%), with most cases showing partial resolution by the last follow-up.

Conclusion: We reported that the incidence of ICI-related CVAEs in the Chinese institution was higher than that in some prior studies. Adherence to guidelines for managing ICI-related CVAEs is found to be suboptimal in real-world practice and highlighted as a needed improvement.

Keywords: immune checkpoint inhibitors, cardiotoxicity, retrospective study

Introduction

During the past decade, the introduction of a novel category of drug termed immune checkpoint inhibitors (ICIs) has transformed the treatment paradigm in the oncology field. ICIs are developed to block immune-evasive signaling and enhance anti-tumor immunity by targeting regulatory proteins, namely immune checkpoints, such as cytotoxic T lymphocyte protein 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1).[1] Nowadays, ICIs have become a pillar in the cancer treatment landscape, with expanding indications approved for a diverse spectrum of solid and hematological malignancies, especially for lung cancer, hepatocellular carcinoma, as well as lymphoma.[2]

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Nevertheless, to achieve a durable anti-tumor response, the systemic augmentation of the immune response may trigger an "off-target" effect resulting in immune-related toxicity distinct from conventional chemotherapy,[3] referred to as immune-related adverse events (irAEs). IrAEs may potentially affect virtually any organ system, involving the skin, endocrine system, gastrointestinal tract, liver, and lungs, yet typically manageable.[4]

Albeit rare, cardiotoxicity associated with ICIs can be challenging for physicians to identify and manage, as it may range from subclinical symptoms to rapidly progressive disorders resulting in devastating consequences.[5] ICI-related cardiovascular adverse event (CVAE) was previously recognized as immune-mediated myocarditis.[6] However, as cumulatively understood, this clinical entity was further defined with an extended spectrum of cardiovascular complications, including pericardial disease, conduction abnormalities or arrhythmias, heart failure, coronary events, and cardiomyopathy.[7] However, due to the potential minimization of specific cardio-surveillance in oncologic trials,[8] the actual cardiotoxicity for ICIs treatment was assumed to be underestimated.[9] Therefore, the incidence of ICI-related CVAEs still seemed unclear,[10] which was reported at 2.09% to 14.6% by heterogeneous studies, including pharmacovigilance analysis of adverse drug events reporting database, meta-analysis, and retrospective cohort studies.[11–16]

Meanwhile, despite the increasing National Medical Products Administration (NMPA) approval of ICIs, including the domestic agents (eg, toripalimab, sintilimab, camrelizumab, and tislelizumab) and a broader use in China,[17] there is limited information profiling the cardiovascular safety resultant from ICIs therapy among the developing country's population. To this end, we conducted a study and attempted to help fill the relevant knowledge gap in the Chinese population.

Materials and Methods

Study Patient Population and Treatment

This retrospective observational study was conducted at a tertiary care hospital in eastern China, which admitted approximately 15000 oncologic patients under treatment annually. We conducted the study based on extracted data from the local prescribing auditing system and electronic medical records (EMR) database. Patients hospitalized from March 1, 2020, to March 31, 2021, who received at least one dose of ICI therapy, were included in the study. The prescribed ICIs agents comprised six anti-PD-1 agents: nivolumab, pembrolizumab, camrelizumab, tislelizumab, sintilimab, and toripalimab, as well as one anti-PD -L1 agent durvalumab. Patients lacking baseline clinical materials such as previous chemotherapy history, accurate cardiovascular comorbidities information, initial ICI treatment data, or lost to follow-up were excluded.

The study protocol was approved by the medical ethics committee of Huzhou Central Hospital (IRB:202205014-01), and the requirement for informed consent was waived in view of the retrospective design. We state that our study was conducted in accordance with the Declaration of Helsinki, and the confidentiality of patients was protected.

Data Collection

Data collection was carried out by two reviewers independently, using a standard data extraction electronic form. A baseline of demographic characteristics and cardiac-specific clinical status was depicted at the initiation of ICI treatment. Data collected included age, sex, race, primary malignancy diagnosis, and stage, ICIs treatment regimens (monotherapy, combination with chemotherapy or radiotherapy), cardiovascular comorbidities, electrocardiograms (ECGs), echocardiograms, serum cardiac biomarkers involving troponin I and B-type natriuretic peptide (BNP). Predefined cardiovascular comorbidities included established coronary artery disease, cardiomyopathy, diabetes, hypertension, cardiac arrhythmias, or heart failure. In addition, we retrospectively collected data on cardiac parameters post-treatment, including (1) regular cardiac work-up such as laboratory tests (troponin I and BNP), electrocardiographic and echocardiographic variables, (2) cardiac magnetic resonance (CMR), and endomyocardial biopsy, if available. We also recorded clinical notes referring to abnormal cardiac presentations, cardiology consultation notes, new diagnoses denoting the predefined CVAEs at discharge, timing at CVAEs, management for CVAEs, and outcome of CVAEs.

According to the International Classification of Diseases, tenth revision, Clinical Modification (ICD-10-CM) diagnosis codes, all those involved diagnoses were regulated.

Diagnosis, Assessment, Grade, and Outcome of CVAEs

According to the recently updated clinical practice guideline of the American Society of Clinical Oncology (ASCO)[18] definition, the primary endpoint of this study focused on ICI-related cardiotoxicity, including myocarditis, heart failure, conduction abnormality, pericarditis, pericardial effusions, and acute coronary syndrome. Criteria for diagnosing the aforementioned cardiovascular complications referred to the 2022 International Cardio-oncology Society (IC-OS) consensus statement for defining cardiovascular toxicities of cancer therapies.[19] As specifically stated, the criteria for myocarditis related to ICI can either be a pathohistological diagnosis by biopsy of cardiac tissue samples or a clinical diagnosis established by a troponin elevation (new, or significant change from baseline) combined with a constellation of clinical syndromes and ancillary examinations. The latter is specified in the IC-OS consensus statement and held to be more applicable in our clinical setting.

A specialized cardiology pharmacist and a cardiologist independently screen all emerging pertinent CVAEs. We reviewed the charts of enrolled patients by checking cardiology diagnostic workups, clinical notes, cardiology consultation notes, or new diagnoses of predefined endpoints at discharge. Laboratory test abnormality was defined as serum troponin I level elevated to ≥the cutoff value of 0.04 ng/mL(positive), and BNP level elevated to ≥100 pg/mL. New-onset ECG abnormalities included atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, and conductive abnormality. Imageological abnormalities included a left ventricular ejection fraction (LVEF) reduction of >10% to a lower normal limit in an echocardiogram or a late gadolinium enhancement in a CMR examination. Clinical notes typically suggestive of suspicious cardiac symptoms included edema, orthopnea, dyspnea, bilateral lower-limb swelling, ankle swelling, palpitation, chest pain, or syncopal attack. All the patients clinically suspected of myocarditis were ruled out of coronary artery disease by coronary angiography or computed tomography angiography.

As for determining the causality between the ICIs treatment and the identified CVAEs, the Naranjo adverse drug reaction algorithm[20] was applied to rate the likelihood of each case by two pharmacists separately. The documented cardiovascular disorder events scored above 5 by the Naranjo algorithm, namely probably or definitely attributable to ICIs administration, were defined as ICI-related CVAEs in our study. The identified CVAEs were assessed and stratified into grade 1–4 in light of the ASCO guideline,[18] mainly based on cardiac biomarker testing, ECG abnormalities, and clinical severity of cardiovascular symptoms.

The outcome of CVAEs was stratified into three grades: complete resolution, partial resolution, or no resolution. Complete resolution was defined as no further symptoms or test results indicating CVAE; partial resolution as one symptom or test result indicating CVAE yet severity has improved; no resolution as symptoms and test results continue at the same frequency and severity or worsen. The follow-up work was based on reviewing the integrated medical record of outpatient and inpatient at an interval of no longer than one month. In case the clinical material is unavailable during the defined frequency, a follow-up by telephone should be conducted. Mortality data, if any, were gathered from medical records or confirmed by telephone. We followed up on the identified CVAEs from the onset presentation to February 28, 2022.

Statistical Analysis

Continuous variables are presented as mean ± SD or median (interquartile range, IQR) as appropriate for the dataset, and the categorical variables are presented as frequencies (percentages). Categorical data were compared using the chi-square test or Fisher's exact test. Continuous variables were compared using unpaired Student's t-tests or Mann–Whitney *U*-test depending on normally distributed conditions. All tests were two-tailed, and *P*-value <0.05 assumed statistical significance. Biologically plausible variables, potential confounders (variable seems to significantly differ across the groups), and/or those with *P*-values of <0.2 were controlled in the multivariate logistic regression models. Statistical analyses were conducted using IBM SPSS Statistics 25 (IBM Corp, Armonk, NY) software.

Missing data, if any, were handled by complete case analysis, namely individuals with missing data on the included variables were dropped from the analyses.

Results

Patients' Characteristics

In total, 203 eligible patients who received ≥1 dose ICI therapy were enrolled during the study duration (Figure 1), of whom 9 patients developed CVAEs probably associated with ICIs and were monitored over a median of follow-up 8 months (IQR, 6–12).

The demographic and clinical baseline of the patients is summarized in Table 1. Compared to non-CVAE patients, patients encountering ICI-related CVAEs were older (63.7±9.7 years versus 73.6±9.2 years, p = 0.03), and concomitant with hypertension (p= 0.02) or heart failure (p=0.01). Sex, diabetes mellitus, or coronary artery disease were not statistically different between the groups. Sintilimab, tislelizumab, camrelizumab, pembrolizumab, toripalimab, nivolumab, and durvalumab were prescribed, by proportion 24.1%, 22.7%, 18.7%, 18.7%, 11.3%, 2.5%, and 2%, respectively.

The overall incidence of CVAEs related to ICI therapy was 4.4% (9/203), and a separate incidence was 8.7% (4/46) for tislelizumab, 7.9% (3/38) for pembrolizumab, 2.6% (1/39) for camrelizumab, 2.0% (1/48) for sintilimab and none in nivolumab, toripalimab, durvalumab, respectively. Yet, the significance of the statistical comparison of the involved ICI agents was unable to be determined due to the limited sample size. The most common indications for ICIs treatment in our cohort were non-small cell lung cancer, esophagus cancer, and gastric cancer, by a proportion of 53.2%, 8.9%, and 6.4%, respectively. A statistically different proportion of primary malignancy was not found between the two groups.

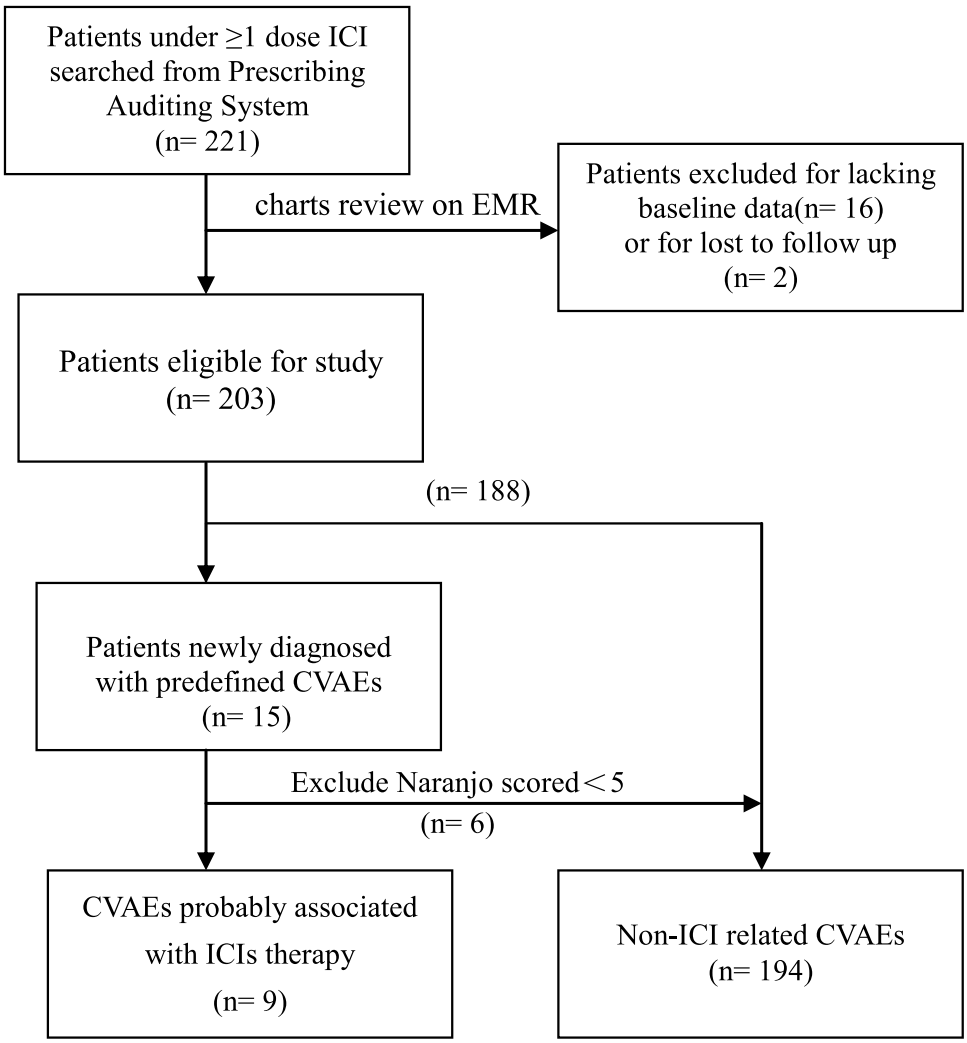

Figure 1 Flowchart of Patient Selection and Outcome Assessment for ICI-Related CVAEs.
Abbreviations: ICI, immune checkpoint inhibitor; EMR, electronic medical record; CVAE, cardiovascular adverse event.

Table 1 Comparison of Patients Receiving Immune Checkpoint Inhibitors (ICIs) with and without Cardiovascular Adverse Events (CVAEs)

Variables	ICI-CVAEs (n=9)	Non-ICI-CVAEs (n=194)	*p* -value
Age (years)	73.6±9.2	63.7±9.7	0.003
Male, n(%)	7(77.8%)	164(84.5%)	0.635
Race (Han)	9(100%)	194(100%)	>0.999
Cardio-Risk comorbidities			
Diabetes mellitus	0(0%)	19(9.8%)	>0.999
Hypertension	6(66.7%)	54(27.8%)	0.02
Heart failure	2(22.2%)	2(1.0%)	0.010
Coronary artery disease	2(22.2%)	8(4.12%)	0.07
ICI-based treatment regimen			
ICI mono therapy	5(55.6%)	48(24.7%)	0.058
ICI combined with chemotherapy	4(44.4%)	137(70.6%)	0.135
ICI combined with radiotherapy	0	9(4.6%)	>0.999
Type of ICI, n			
Nivolumab	0	4	
Pembrolizumab	3	35	
Camrelizumab	1	37	
Tislelizumab	4	42	
Sintilimab	1	48	
Toripalimab	0	23	
Durvalumab	0	5	
Type of cancer, n (%)			
Lung cancer	7(77.8%)	101(52.1%)	0.178
Gastric cancer	1(11.1%)	12(6.2%)	0.456
Esophagus cancer	1(11.1%)	17(8.8%)	0.574

Abbreviations: ICIs, immune checkpoint inhibitors; CVAEs, Cardiovascular adverse events.

Clinical Characteristics, Treatment, and Outcome of Cardiovascular Adverse Events Associated with ICIs

Nine patients were identified as developing CVAEs probably out of ICI therapy, including heart failure (n = 3), arrhythmia (n = 2), myocarditis (n = 2), and pericarditis or pericardial effusion (n = 2). Characteristics, presentations, and management of the 9 cases are described in Table 2.

The median score of the Naranjo algorithm for assessing the causality was 6 (min: 5, max: 8). The median onset time of CVAEs was 63 days (IQR, 29–74) from the initiation of ICI treatment. Among the identified 9 cases, grade 3 and/or grade 4 accounted for 66.6%. The initial clinical presentations were mostly atypical, including breathlessness or dyspnea (66.6%) and fatigue (33.3%), which could be overlapped with the primary diseases.

Management of CVAEs included suspending (n = 5) or discontinuing ICIs treatment (n = 4), symptomatic therapy (n = 4), and corticosteroid-based immunosuppressive therapy (n = 2). Nevertheless, concerning Grade 3 or Grade 4 CVAEs, only 3 cases (50%) permanently discontinued with ICI, which was suggested by the ASCO guideline.[21] One patient encountering myocarditis received a lower dose of steroid than the ASCO guideline advised. The overall adherence to guidelines for managing ICI-related CVAEs was approximately 44% (4/9). Most CVAEs came out with partial resolution at the last follow-up. A case of acute pericardial effusion died but probably of a thrombotic complication.

Discussion

Since ICI is one of the most promising antineoplastic therapeutic approaches, it could be expected that an increasing number of cancer patients are eligible for ICI treatment in developed countries and China.[21] There are a total of eleven

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Table 2 Characteristics, Management and Outcome of Patients Developed Cardiovascular Adverse Events (CVAEs)

NO.	CVAE	Age	Sex	Primary Diagnosis	ICI-based Treatment Regimen	Presentation (Concurrent irAEs)	Naranjo Score	Time to onset (Days)	Grade	Management	Outcome of CVAEs	Follow Up
1	**HF**	73	F	Gastric cancer	P	Hypotension, dyspnea, elevated serum BNP level, LVEF reduced >10% from baseline	7	76	4	Withholding ICI, diuretic and symptomatic therapy with inotropes	Partial resolution	She resumed ICI therapy one month later under close monitoring
2	**HF**	88	M	NSCLC (squamous carcinoma)	T	Ankle swelling, fatigue, chest distress, elevated serum BNP level,	6	12	3	Withholding ICI, decongestive and symptomatic therapy.	Partial resolution	He continued ICI therapy for 4 cycles until disease progression
3	**HF**	80	F	Esophagus cancer	T+ Capecitabine	Breathless, elevated serum BNP level,	5	93	3	Decongestive and symptomatic therapy.	Partial resolution	She discontinued ICIs therapy due to disease progression
4	**Arrhythmia**	75	M	NSCLC (adenocarcinoma)	P +Carboplatin + Paclitaxel (Albumin bound)	Concurrent with cutaneous irAE, asymptomatic, new-onset atrial fibrillation diagnosed by ECG test	6	73	2	Observing and closely monitoring.	Complete resolution	He continued ICI therapy for another 2 cycles and discontinued due to a bone marrow suppression.
5	**Arrhythmia**	70	M	NSCLC (adenocarcinoma)	C +Carboplatin + Paclitaxel (Albumin bound)	Asymptomatic, second-degree type I AV-Block diagnosed by ECG test	5	66	2	Observing and closely monitoring.	No resolution	He continued ICI therapy for another 7 cycles.
6	**Myocarditis**	70	M	NSCLC (squamous carcinoma)	T	Fatigue, breathless, serum TnI level increased to 2 ULN, elevated serum BNP level, LVEF reduced >10% from baseline	8	63	3	Suspending ICI therapy, excluding coronary artery events, intravenous methylprednisolone 40 mg daily for three days and orally tapering for 90 days to a total dose of 1000 mg methylprednisolone	Complete resolution	He rechallenged with ICI therapy 6 months later for another 3 cycles, pretreated with a moderate dose of methylprednisolone.

7	**Myocarditis**	83	M	NSCLC (adenocarcinoma)	P(half dose) +Carboplatin + Paclitaxel (Albumin bound)	Concurrent with cutaneous irAE and ICI-P, fatigue, palpitations,TnI level increased to 4ULN, new-onset complete RBBB, LVEF level maintained>50%	7	46	3	Suspending ICI therapy, excluding coronary artery events, intravenous methylprednisolone 40 mg daily for five days without a pulse dose and tapering steroid therapy	Partial resolution	He was withheld with ICI and intravenously given a moderate dose (40 mg) of methylprednisolone daily for five days without a pulse and tapering steroid therapy. Outpatient follow-up showed a sustained positive level of troponin I. After 3 months, he was readmitted and given methylprednisolone 40 mg intravenously daily for 3 days. At discharge, he was under GDMT for HF and switched to radiotherapy.
8	**Pericarditis**	64	M	NSCLC (squamous carcinoma)	S	Chest pain, diffuse saddle-shaped ST elevation on ECG, new pericardial effusion on echocardiograms test	6	4	2	Observing and closely monitoring, excluding pseudo progression	Partial resolution	He discontinued ICI therapy permanently and switched to radiotherapy.
9	**Pericardial effusion**	59	M	NSCLC (squamous carcinoma)	T	Pericardial effusion mounted abruptly 2 days later after the fourth dose ICI administration according to chest X-ray	5	52	3	Symptomatic treatment without cardiac drainage.	Unknown	He died one day later, probably of a thrombotic complication.

Abbreviations: irAEs, immune related adverse events; HF, heart failure; ECG, electrocardiogram; AV, atrio-ventricular; ICI, immune checkpoint inhibitor, M, male; F, female; NSCLC, non-small cell lung carcinoma; P, pembrolizumab; C: camrelizumab; T, tislelizumab; S, sintilimab; LVEF, Left ventricular ejection fraction; BNP, B-type natriuretic peptide; inhibitor; TnI: troponin I;ULN, upper limit of normal; ICI-P, immune checkpoint inhibitor-related pneumonitis; RBBB, right bundle branch block; IV, intravenous; GDMT, guideline directed medical therapy.

types of domestic and five types of abroad ICIs approved by NMPA up to Dec 31, 2022,[22] and widely used both in curative and palliative settings. Our study mainly focused on the cardiotoxicity associated with ICIs, with four domestic anti-PD-1 agents encompassed. In this cohort, we reported that the incidence of ICI-related CVAEs was 4.4%, and adding chemotherapy to the ICI treatment may not increase the incidence of CVAEs. In addition, we revealed that management for ICI-related CVAEs might not completely comply with the guidelines in real-world practice.

The holistic incidence of ICI-related CVAEs in cohort studies ranged from 3.9% to 14.6%,[14,16,23] which could be interpreted by discrepancies in study design, endpoint definition, assessment method, and types of ICIs involved. Concerning those issues, we explored some different strategies in this study. First, as for study design, we applied the approach of manual charts review rather than ICD data review employed by previous studies,[16,23] as the latter was implied to perform imprecisely in evaluating irAEs.[24] Additionally, we excluded vasculitis or venous thromboembolism (VTE) from the study endpoint definition, in view that attributing VTE to ICI therapy was controversial.[25,26] VTE accounted proportionately for the reported incidence of CVAEs in some studies.[12,14] However, it was usually difficult to differentiate thrombotic events induced by ICI therapy from the cancer-associated hypercoagulable state.[27] Furthermore, it is generally acknowledged that CVAEs in cancer patients may arise from the disease itself or the therapy other than ICIs, contributing to compromise the causal inference of the study.[28] Thus, to rule out the alternative cause responsible for CVAEs, we introduced the Naranjo algorithm to ascertain the causality between the identified events and ICI exposure. A total of 6 CVAEs scored <5 by the Naranjo algorithm were ascribed as less likely to be linked to ICI therapy and thereby excluded. For instance, one case developing new-onset atrial fibrillation (Naranjo scored=4) was excluded for concurrently prescribed with recombinant human interleukin-11 (rhIL-11), a well-recognized drug associated with atrial fibrillation.[29] As a result, the investigators finally adjudicated 9 cases of CVAEs probably related to ICI therapy.

Our results suggest that patients with certain cardiovascular risks, such as hypertension and heart failure, may have an increased risk of CVAEs, while diabetes mellitus is not recognized as a predisposing factor in this study. The partial inconsistency with previous findings[16,30] could be explained by a discrepancy in the study design and the number of included patients. Still, some perspectives held that pre-existing cardiovascular diseases with myocardial injury, such as heart failure and myocardial infarction, were at risk for ICI-related CVAEs.[31] Moreover, atherosclerosis, the underlying pathophysiological mechanism shared by most cardiovascular risk factors, was revealed to be negatively regulated by CTLA-4 and PD-1/PD-L1 axes.[32] Accordingly, ICI-induced inflammatory response might accelerate atherosclerosis and increase cardiovascular risk over a longer time, as indicated by a recent study.[33] Howsoever, related cardiovascular risk that may contribute to the ICI-mediated cardio-toxic effect was not yet explicitly elucidated and should be expounded through additional studies.

Compared with ICI monotherapy, additional CVAE risk associated with ICI plus chemotherapy was of concern in the study as well, as the latter treatment regimens commonly contained types of acknowledged cardio-toxic drugs such as taxanes and platinum.[34] Intriguingly, increased CVAE rates were not observed regarding the combination of chemotherapy with ICI. The possible mechanism was that the immunosuppression from cytotoxic agents might alter the immune environment and inhibit the overactive immune response, thereby reducing the rate of irAEs,[35] which was partly verified by recent meta-analyses in respect of pneumonitis and skin reactions.[36,37] We suggest more insight should be put into this issue and confirm our findings, as ICI plus chemotherapy is preferred for a considerable quantity of cancer patients.

In addition, a clinical implication for managing ICI-related CVAEs should be noted. As for ICI-related myocarditis, an intractable issue, we presented two cases under discrepant steroid therapy, leading to different outcomes. The diagnosed cases (case 6 and case 7, detailed in Table 2) were characterized by slight troponin I elevation and subacute clinical manifestation. They both discontinued ICI treatment and received a moderate dose of methylprednisolone for 3–5 days in hospital. Case 6 was sequentially tapering methylprednisolone under close troponin I monitored for a duration of 90 days at a total dose of 1000 mg. Six months later, he resumed ICI treatment for another three cycles and obtained a therapeutic response. While case 7, sparing from a sequential steroid therapy at discharge, was readmitted three months later and diagnosed with relapsed acute cardiac dysfunction. After a 15-day hospital stay of symptomatic treatment and moderate steroid therapy, he received a guideline-directed medical therapy for heart failure to reduce the residual risk of sequela and was restrained from ICI therapy.

It was previously revealed that clinical practice for handling ICI-related CVAEs might not comply with the guidelines thoroughly in real world,[38] as observed in our study. A lack of awareness about guidelines may partly explain since recognizing and managing irAEs is a cross-discipline task.[19] Relevant diagnostic resources for irAEs are sometimes constrained, resulting in insufficient screening and a treatment delay. Specifically, there were some barriers to optimal adherence to steroid treatment for ICI-related cardiotoxicity.[39] The guidelines advocate an initial high-dose and adequate duration of steroids should be administered as a first-line strategy to patients with grade ≥2 ICI-related myocarditis.[18,40] However, clinical hesitation arises from concern that high-dose or prolonged use of steroids might negatively impact prognosis by dampening the antitumor efficacy[41] or inducing adverse effects.[42] Actually, some studies have implied that steroids due to irAEs did not undermine the overall survival outcome,[43] whereas a high dose use significantly improved the cardiac outcome of ICI-related myocarditis and refrained from an antitumor treatment interruption.[30] Our findings substantiate the view that an adequate dose and duration of steroids should be given at the early onset of immune-mediated events; otherwise, the residual T-cell overactivation could linger smolderingly and flare unexpectedly.[44]

Given that CVAEs related to ICIs remain a "tricky business" in current clinical scenarios, a feasible algorithm for managing this issue should be established and validated, particularly in resource-limited settings where cardiac MRI or endomyocardial biopsy is inaccessible. It is commonly recommended that the baseline of cardiovascular risk on the basis of ECG, troponin assay, and relevant symptoms be assessed prior to ICI therapy.[45] Routine surveillance on the serial troponin (locally available) for patients at high risk is preferable in dynamically evaluating cardiovascular prognosis and guiding a steroid treatment regimen for irAEs, which could be applied to the identified CVAEs in our study.

However, the threshold of the troponin baseline and elevation rate to detect cardiovascular risk in the population under ICI therapy should be determined by further research focusing on the clinical utility of cardiac biomarkers.[45] Meanwhile, the therapeutic application of steroids and non-steroid targeted agents for ICI-related myocarditis needs to be further delineated by well-designed prospective studies.[39] Additionally, an emerging discipline of cardio-oncology, which is yet in its infancy in China,[46] is called to facilitate the improved management of this conundrum.

Our study has limitations. First, due to the inherent nature, our retrospective study might be prone to bias from irregular cardiac monitoring data at the clinician's discretion for review. Second, due to the small sample size of the ICI-CVAEs group, the potential confounders could not be determined significantly on the multivariate logistic regression analysis and might not be adequately controlled. Besides, our duration of follow-up might be limited for detecting the long-term cardiovascular outcome of patients exposed to ICIs treatment. Moreover, as our study was conducted in a single institution, the sample size was relatively small, while available types of ICIs and eligible patients were not enough to provide a complete view of ICI-related CVAEs. As such, multicentre, prospective studies and registries with larger cohorts will be needed to further address the issues of ICI-related CVAEs with respect to incidence, predictors, and optimized management. Still, we quantitatively complemented real-world data regarding ICI-related CVAEs among the Chinese population and brought some clinical implications.

Conclusion

This study finds that the incidence of ICI-related CVAEs in the Chinese institution was higher than some studies previously reported. Adherence to guidelines for managing ICI-related CVAEs appeared to be suboptimal in real-world practice, resulting in unfavorable cardiac outcomes. Some actions, such as a multidiscipline team or cardio-oncology training, should be taken to improve guideline adherence. Routine cardiac surveillance should be implemented for patients receiving ICI therapy at high risk of CVAEs, though the risk should be determined by further research.

Ethics Approval and Informed Consent

The study protocol was approved by the institutional ethics committee (IRB:202205014-01), and the requirement for informed consent was waived in view of the retrospective design.

Disclosure

The authors report no conflicts of interest in this work.

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