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ORIGINAL ARTICLE

A retrospective cohort study on the cardiotoxicity incidence rates of immune checkpoint inhibitors for oncology patients

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Abstract

Background: This present study investigated the incidence rates of cardiotoxicity among cancer patients treated with immune checkpoint inhibitors (ICIs) plus other anticancer drugs.

Methods: This was a retrospective hospital-based cohort study using the medical records and the Cancer Registry records from the Taipei Veterans General Hospital. We enrolled patients diagnosed with cancer between 2011 and 2017, who were over 20 years old and had received ICI therapy, including pembrolizumab, nivolumab, atezolizumab, and ipilimumab. Cardiotoxicity was defined by the diagnosis of myocarditis, pericarditis, arrhythmia, heart failure, and Takotsubo syndrome.

Results: We identified 407 patients who were eligible to participate in this study. We defined the three treatment groups as follows: ICI therapy, ICI combined with chemotherapy, and ICI combined with targeted therapy. Using ICI therapy as a reference group, the cardiotoxicity risk was not significantly higher compared to the ICI combined with chemotherapy group (adjusted hazard ratio 2.1, 95% confidence interval 0.2–21.1, $p = 0.528$] or to the ICI combined with targeted therapy group (adjusted hazard ratio 1.2, 95% confidence interval 0.1–9.2, $p = 0.883$). The total incidence rate of cardiotoxicity was 3.6 of 100 person-years, indicating an average incidence time of 1.0 ± 1.3 years (median: 0.5 years; range: 0.1–4.7 years) for 18 cardiotoxicity patients.

Conclusion: The incidence rate of ICI-related cardiotoxicity is low. Combination of ICI with either chemotherapy or targeted therapy might not significantly increase the risk of cardiotoxicities among cancer patients. Nevertheless, it is recommend being careful in patients treated high-risk cardiotoxicity medications to avoid drug-related cardiotoxicity with a combination of ICI therapy.

Keywords: Chemotherapy; Drug-related cardiotoxicity; Immune checkpoint inhibitors; Incidence rate; Targeted therapy

1. INTRODUCTION

In recent years, anticancer treatment has been revolutionized by the development of innovative strategies involving targeted therapies and immunotherapy. Immune checkpoint inhibitors (ICIs) are a class of immunotherapy drugs used to treat or control the proliferation of tumor cells by preventing immunosuppression and revitalizing antitumor immune responses.[1] ICIs are based on various mechanisms. Targeting inhibitory receptors on T cells is cytotoxic T lymphocyte-associated protein-4 (CTLA-4). Programmed cell death protein-1 (PD-1) and PD-1 ligand (PD-L1) bind to the corresponding ligands on tumor cells. In clinical practice, ICIs are used for a variety of cancers, including unresectable or metastatic melanomas, non-small cell lung cancer, Hodgkin's lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, gastric cancer, and liver cancer.

ICIs may lead to the manifestation of immune-related toxicities that can severely affect any organ following ICI administration. The common adverse effects include skin, kidney, lung, and gastrointestinal tract, with hepatitis, pneumonitis, nephritis, myositis, and dermatitis. Most of these toxicities are reversible and can be relieved by glucocorticoid therapy.[2] In general, adverse drug reactions of ICIs are less frequently observed compared to conventional chemotherapy. But, severe cardiovascular immune-related adverse events (irAEs), such as myocarditis, pericarditis, vasculitis, arrhythmia, can be easily ignored.[3,4] Scholars found that tumor cells and cardiomyocytes have similar lymphocytic properties and share antigens with T-cell receptors.[5] It is speculated that ICI-related cardiotoxicity is relevant to PD-L1 and CTLA-4 expression in the cardiomyocytes. PD-L1 inhibitors and CTLA-4 inhibitors would lead to T-cell accumulation and boost T-cell response in the cardiac tissues following by neutrophil, macrophage infiltration.[6,7] Therefore, the injury

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to myocytes expresses as myocarditis, pericarditis, arrhythmia, heart failure, and Takotsubo syndrome.

Although early clinical trials failed to reveal any association between ICIs and myocardial events, increasing evidence from case reports and cohort studies indicates that ICIs are linked to the development of cardiovascular irAEs.[8,9] According to the results of previous systematic reviews and meta-analysis studies, the most common cardiotoxicities are atrial fibrillation, myocarditis, and pericardial effusion. The incidence of these irAEs in the ICI groups was higher compared to non-ICI groups.[10] On the other hand, use of dual ICIs or single ICI has not been associated with an increased risk of cardiovascular irAEs.[11] However, these findings are inconsistent.

In general, combination of anticancer therapies is common use for cancer patients, and they might have potentially higher risks of developing complications when receiving multiple treatments. Most previous studies have revealed the cardiotoxicity between ICI plus chemotherapy or targeted therapy versus chemotherapy or targeted therapy.[10,12–14] A number of chemotherapy and targeted therapy known to be potentially increasing different type of cardiovascular risk. Chemotherapy (eg, anthracyclines, alkylating agents, etc.) directly make permanent myocardial damage and induce heart failure. Targeted therapy (eg, trastuzumab, tyrosine kinase inhibitors, etc.) cause cardiac cells dysfunction temporarily by the mitochondrial system and inhibiting protein synthesis.[15,16] However, it remains safety concerns if ICI combines with chemotherapy or targeted therapy. Therefore, we would like to use the medical record database of oncology patients from a teaching hospital and to investigate the incidence rate of cardiotoxicity among patients treated with the ICI therapy, ICI combined with conventional chemotherapy or ICI combined with targeted therapy. Besides, we considered the demographics, comorbidities, physical status, personal behaviors, and medical care factors to reduce the impact of potential confounding factors in this cohort.

In addition, according to previous studies, the correlation between ICI therapy and drug-related cardiotoxicity, whether single ICI or combination regimens, remains controversial. Most studies have examined the relative risks (RRs) or odds ratios (ORs) to evaluate ICI-induced cardiotoxicities.[10,12,13,17,18] However, these studies failed to consider the follow-up time from the initiation of ICI therapy until the occurrence of cardiotoxicity during the treatment period, which might have affected the consistency of their findings. In this study, we analyzed the incidence rate and hazard ratio (HR) in a cohort study that were more accurate to reduce potential bias when evaluating the risk of drug-related cardiotoxicity.

2. METHODS

This cohort study was consistent with the guidelines stated by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (the checklist of cohort studies). This study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital (TVGH) (IRB No. 2019-05-001AC).

2.1. Participants and data collection

This three-arm retrospective hospital-based cohort study was performed at TVGH, in Taiwan. TVGH serves an average of 6500 outpatient visits per day and approximately 3100-bed inpatients, of which >30% are oncology patients.

This cohort study enrolled all participants who were over 20 years of age and were diagnosed with cancer in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 140 to 208 or the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes C00 to D49, between 2011 and 2017.

Inclusion criteria were as follows: patients had received ICI therapy, including anti-PD-1 (pembrolizumab, nivolumab), anti-PD-L1 (atezolizumab), and anti-CTLA-4 (ipilimumab). Among the four ICI agents, ipilimumab was approved by Taiwan Food and Drug Administration in 2014 and atezolizumab was approved in 2017. We retrospectively collected patients' medical records three years before 2014 (since 2011) and tracked four years from 2017 (until December 31, 2021). All patients were divided into three groups: ICI therapy (group 1), ICI combined with chemotherapy (group 2), and ICI combined with targeted therapy (group 3). Chemotherapy included anthracyclines (eg, doxorubicin, epirubicin, etc), alkylating agents (eg, cisplatin, ifosfamide, etc), antimetabolites (eg, gemcitabine, pemetrexed, etc), and taxanes (ie, docetaxel, paclitaxel); targeted therapy included tyrosine kinase inhibitor (eg, lenvatinib, erlotinib, etc), monoclonal antibody (eg, bevacizumab, cetuximab, etc). Combination therapy was defined as concurrent use of two drugs in the same prescription for outpatients and within 1 week for inpatients. Overall, 7987 cancer patients with complete data were identified during our study period in TVGH. Of them, 407 patients received ICI therapy (group 1: n = 315, group 2: n = 59; and group 3: n = 33) (Fig. 1). We excluded patients treated with triple therapy (combination of ICIs, chemotherapy, and targeted therapy) because the sample size was too small (n = 3) to perform a meaningful statistical analysis.

ICI therapy-related cardiotoxicities were identified using the relevant diagnostic codes of ICD-9-CM or ICD-10-CM, as follows: myocarditis (429.0, 422.99, 422.90, I40.8, I40.9, I51.4), pericarditis (420.90, 420.99, I30.8, I30.9), arrhythmia (427.9, I49.9), congestive heart failure (428.0, 428.9, I50.89, I50.9),

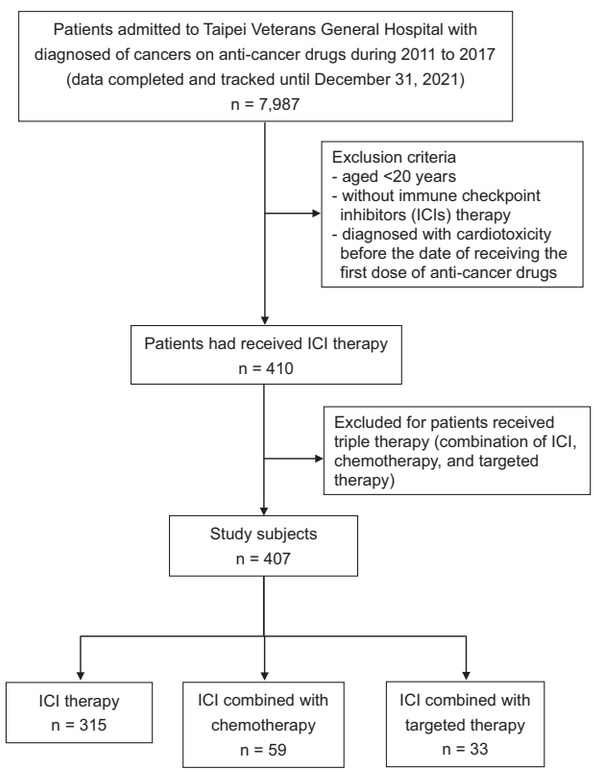

Fig. 1 Selection of study cohort.

and Takotsubo syndrome (429.89, I51.81).[4,19] Patients were excluded if they were aged <20 years, never received an ICI therapy, or had incomplete medical records. Besides, patients who had been diagnosed with myocarditis, pericarditis, arrhythmia, congestive heart failure, and Takotsubo syndrome before receiving the first dose of anticancer drugs were excluded. Those diagnostic codes of ICD-9-CM or ICD-10-CM were mentioned above.

Potential confounding factors considered in this study were sociodemographics (age and gender), comorbidities (hypertension, cardiovascular diseases, chronic kidney diseases, diabetes mellitus, and hyperlipidemia), physical status and personal behaviors (body mass index [BMI], smoking status, alcohol consumer, and betel nut chewing behavior), and medical care factors (combination of other drugs that might worsen cardiac function and radiation therapy). Comorbidities were identified using the relevant diagnostic code of ICD-9CM or ICD-10-CM. We collect the information of physical status, personal behavior, and medical care factors from electronic medical records. We included both inpatients and outpatient visits data from cancer patients. The outpatient follow-up period (return to outpatient clinics) is commonly 28 days per course in this teaching hospital and most of enrolled participants were outpatients. Therefore, both inpatients and outpatient visits, we defined concurrent use of the other medicines that were used within 28 days after the first dose of anticancer drugs.

Cancer patients might be hospitalized for critical conditions or other comorbidities, so they would receive corticosteroids treatment (eg, methylprednisolone) for a short period of time. On the other hand, corticosteroids may be used as antiemetic agents (eg, dexamethasone) for chemotherapy-induced nausea and vomiting during patients' chemotherapy regimen, besides NSAIDs are commonly used as analgesics for cancer patients. Because the concurrent use of medications worsening or protecting cardiac function is very challenging to assess, it is difficult to include all of those drugs. Accordingly, we only selected the most commonly used medications, NSAIDs and corticosteroids, as concurrent use of other medications in this study.

2.2. Statistical analysis

Confounders of the three groups, ICI therapy, ICI combined with chemotherapy, and ICI combined with targeted therapy were compared. Continuous variables were described as mean ± standard deviation, and categorical variables were described as sample numbers and percentages. In univariate analysis, a one-way analysis of variance (ANOVA) was used for continuous variables (age and BMI), and the Pearson's Chi-squared test was assessed for categorical variables (gender, personal history, comorbidity, concurrent use of other medications, and radiation therapy). Logistic regression and Cox regression were both analyzed in this study. We estimated the adjusted RR (aRR), the adjusted HR (aHR), and relevant 95% confidence intervals (CIs) for cardiotoxicity in ICI combination treatment groups by comparing with the ICI therapy, adjusting for betel nut chewing behavior, hyperlipidemia, and concurrent use of other medications. The level of significance was set at 0.05. All statistical analyses were conducted by the SPSS software (IBM Corp, Somers, NY, USA).

3. RESULTS

3.1. Patient characteristics

The average follow-up period of 1.2 ± 1.4 years (median: 0.7 years; range: 0–6.1 years) for the study subjects. Of 407 patients, 87 (21.4%) had lung cancer, 71 (17.4%) had liver cancer, 51 (12.5%) had gastrointestinal cancers, and the remaining were renal cancer (6.9%), head and neck cancers (6.1%), urothelial carcinoma (6.1%), etc. Table 1 demonstrates the distribution of the included patients. ICI therapy was a majority (77.4%), followed by ICI combined with chemotherapy (14.5%), and ICI combined with targeted therapy (8.1%). One patient received ICI combined with chemotherapy for 4 weeks followed by 18 weeks of ICI combined with targeted therapy. Another patient received ICI combined with chemotherapy once after ICI combined with targeted therapy. They were included in the ICI combined with the targeted therapy group. In addition, they did not experience drug-related cardiotoxicity. Among them, there were 158 (38.8%) male and 249 (61.2%) female subjects. The mean ages of the three groups were 61.5 ± 13.4, 61.2 ± 12.0, and 64.0 ± 10.7 years, respectively. The mean BMI was similar among the three groups. There was a significant difference ($p < 0.05$) in betel nut chewing behavior history, hyperlipidemia, and concurrent use of other medications among the three groups: both betel nut chewing behavior history and hyperlipidemia for the highest proportion (21.2%) of the ICI combined with targeted therapy group, and two-thirds (66.1%) of the ICI combined with the chemotherapy group were patients with concurrent use of other medications. The proportion of concurrent use of other medicines in ICI combined with chemotherapy group was significantly higher than in ICI combined with the targeted therapy group or ICI therapy group (66.1% vs 21.2%, 29.8%, $p < 0.0001$). The detail of concurrent use of drugs listed in Supplementary Table 1, http://links.lww.com/JCMA/A183.

3.2. Cardiotoxicity risk

We identified 18 subjects (4.4%) who developed cardiotoxicity, including 13 subjects (ten with heart failure and three with arrhythmia) in the ICI therapy group, four subjects (three with heart failure and one with arrhythmia) in the ICI combined with the chemotherapy group, and one subject had heart failure in the ICI combined with the targeted therapy group (Supplementary Table 2, http://links.lww.com/JCMA/A184). Using ICI therapy as the reference group, while adjusting for confounders (betel nut chewing behavior, hyperlipidemia, and concurrent use of other medications), aRR was not significantly higher in subjects receiving ICI combined use with chemotherapy (aRR 2.4, 95% CI 0.6–7.0, $p = 0.255$). On the contrary, the ICI combined with targeted therapy group had a lower aRR (aRR 0.6, 95% CI 0.1–5.3, $p = 0.686$). The total incidence of cardiotoxicity was 4.4 per 100 persons (Table 2). The detail information of concurrent use of other medications in Supplementary Table 3, http://links.lww.com/JCMA/A185.

In addition, after considering the duration of follow-up, the cardiotoxicity risk was not significantly higher in subjects receiving ICI combined use with chemotherapy (aHR 2.1, 95% CI 0.2–21.1, $p = 0.528$) and ICI combined with targeted therapy (aHR 1.2, 95% CI 0.1–9.2, $p = 0.883$) compared to the reference group (Table 3). The incidence rate represented the original proportion of person-years. During 500 person-years of follow-up, the total incidence rate 3.6 per 100 person-years, including 3.2 per 100 person-years in the ICI therapy group, 5.4 per 100 person-years in the ICI combined with chemotherapy group, and 4.0 per 100 person-years in the ICI combined with targeted therapy group, respectively. The average of incidence was 1.0 ± 1.3 years (median: 0.5 years; range: 0.1–4.7 years) for 18 patients with cardiotoxicity.

4. DISCUSSION

To the best of our knowledge, this is the first hospital-based retrospective cohort study to investigate the incidence rate of cardiotoxicity outcomes among cancer patients receiving a

Table 1

Variables comparison on confounding factors among treatment groups

Variables	ICI therapy (n = 315) n (%)/mean ± SD (min, max)	ICI combined with chemotherapy (n = 59) n (%)/mean ± SD (min, max)	ICI combined with targeted therapy (n = 33) n (%)/mean ± SD (min, max)	f/Chi-square	*p*
Gender					
Male	119 (37.8)	27 (45.8)	12 (36.4)	1.425	0.490
Female	196 (62.2)	32 (54.2)	21 (63.6)		
Age, y	61.5 ± 13.4 (20, 92)	61.2 ± 12.0 (23, 87)	64.0 ± 10.7 (37, 85)	0.587[a]	0.556
Body mass index	21.8 ± 4.1 (12.5, 35.5)	21.3 ± 3.1 (13.7, 28.4)	21.7 ± 3.8 (15.0, 28.7)	0.491[a]	0.612
Personal history					
Smoking status					
Never	180 (57.1)	35 (59.3)	17 (51.5)	0.537	0.764
Former or current	135 (42.9)	24 (40.7)	16 (48.5)		
Alcohol consumer					
Never	221 (70.2)	40 (67.8)	21 (63.6)	0.669	0.716
Former or current	94 (29.8)	19 (32.2)	11 (36.4)		
Betel nut chewing behavior					
Never	267 (84.8)	57 (96.6)	26 (78.8)	7.341	0.025[b]
Former or current	48 (15.2)	2 (3.4)	7 (21.2)		
Death					
No	68 (21.6)	9 (15.3)	2 (6.1)	5.365	0.068
Yes	247 (78.4)	50 (84.7)	31 (93.9)		
Comorbidity					
Hypertension					
No	241 (76.5)	48 (81.4)	25 (75.8)	0.702	0.704
Yes	74 (23.5)	11 (18.6)	8 (24.2)		
Cardiovascular disease					
No	274 (87.0)	54 (91.5)	32 (97.0)	3.554	0.169
Yes	41 (13.0)	5 (8.5)	1 (3.0)		
Chronic kidney disease					
No	301 (95.6)	54 (91.5)	30 (90.9)	2.532	0.282
Yes	14 (4.4)	5 (8.5)	3 (9.1)		
Diabetes					
No	266 (84.4)	51 (86.4)	29 (87.9)	0.387	0.824
Yes	49 (15.6)	8 (13.6)	4 (12.1)		
Hyperlipidemia					
No	290 (92.1)	57 (96.6)	26 (78.8)	9.097	0.011[b]
Yes	25 (7.9)	2 (3.4)	7 (21.2)		
Concurrent use of other medications[c]					
No	221 (70.2)	20 (33.9)	26 (78.8)	31.721	<0.000[b]
Yes	94 (29.8)	39 (66.1)	7 (21.2)		
Radiation therapy					
No	119 (37.8)	21 (35.6)	11 (33.3)	0.320	0.852
Yes	196 (62.2)	38 (64.4)	22 (66.7)		

[a]Age and body mass index were analyzed by ANOVA; other categorical variables were analyzed by the Chi-squared test.

[b]$p < 0.05$.

[c]Nonsteroid anti-inflammatory drugs and corticosteroids were used within 28 days after the first dose of anticancer drugs.

ICI = immune checkpoint inhibitor; SD = standard deviation.

combination of ICI therapy and chemotherapy or targeted therapy comparing to the ICI therapy. Our findings reveal that the risk of cardiotoxicity was not increased either in the group of patients undergoing ICI therapy combined with chemotherapy or targeted therapy. In addition, the incidence rate of cardiotoxicity was relatively low.

Previous studies investigating the incidence of cardiotoxicity have demonstrated inconsistent findings. For example, Waheed et al. utilized the electronic health records of a tertiary care center containing information on all patients receiving anticancer drugs, including PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4.[19] Of the 424 patients that had received ICI therapy, 62 (14.62% incidence) patients were diagnosed with cardiotoxicity after the initiation of ICI therapy, and the median time to cardiotoxicity ranged between 30 and 175 days. In another report, Dolladille et al. systematically reviewed all randomized controlled trials investigating cardiovascular adverse events following ICI therapy. The authors estimated the incidence of cardiovasuclar irAEs to be 3.2 per 1000 patients, and the summary OR was 4.42 (95% CI 1.56–12.50, $p < 0.01$).[17] However, our results showed that the incidence of cardiotoxicity was 4.4%. In general, incidence represents the proportion of cases with a disease or adverse event to the total number of subjects included, and thus it does not consider the time-to-onset. Therefore, the disease incidence of different studies vary widely. We consider that it might be inaccurate to solely consider the incidence of drug-related adverse effects in terms of evaluating the safety of drug use in pharmaceutical research.

Nonetheless, our study indicated that Cox regression was a better method compared to logistic regression in analyzing the

Table 2

Comparison on the incidence and relative risk of cardiotoxicity among treatment groups

Treatment group	Incident cases	Persons	Incidence (per 100 persons)	cRR	95% CI	*p*	aRR	95% CI	*p*
ICI therapy	13	315	4.1	1.0 (ref)			1.0 (ref)		
ICI combined with chemotherapy	4	59	6.8	1.7	0.5–5.4	0.374	2.4[a]	0.6–7.0	0.255
ICI combined with targeted therapy	1	33	3.0	0.8	0.1–5.7	0.761	0.6[a]	0.1–5.3	0.686
Total	18	407	4.4						

aRR = adjusted relative risk; cRR = crude relative risk; ICI = immune checkpoint inhibitor.
[a]Adjusted for betel nut chewing behavior, hyperlipidemia, and concurrent use of other medications.

Table 3

Comparison on the person-years incidence rate and hazard ratio of cardiotoxicity among treatment groups

Treatment group	Incident cases	Follow-up duration (person-years)	Incidence rate (per 100 person-years)	cHR	95% CI	*p*	aHR	95% CI	*p*
ICI therapy	13	401	3.2	1.0 (ref)			1.0 (ref)		
ICI combined with chemotherapy	4	77	5.4	1.7	0.2–15.3	0.638	2.1[a]	0.2–21.1	0.528
ICI combined with targeted therapy	1	22	4.0	1.1	0.1–8.3	0.949	1.2[a]	0.1–9.2	0.883
Total	18	500	3.6						

aRR = adjusted relative risk; cRR = crude relative risk; ICI = immune checkpoint inhibitor.
[a]Adjusted for betel nut chewing behavior, hyperlipidemia, and concurrent use of other medications.

risk of drug-related cardiotoxicity. In general, the RR refers to the ratio of two incidences (exposed vs unexposed groups), tested by a logistic regression model, which is a common statistical method used in literature. For example, in this study, Table 2 showed that the crude value of RR (0.8) of ICI combined with targeted therapy is performed from the respective incidences (3.0 divided by 4.1). This finding suggests that ICI combined with targeted therapy had a lower risk of inducing cardiotoxicity compared to ICI therapy. However, the time-to-onset of adverse drug effects varies among patients, thus it should be considered when calculating the incidence rates, also because it could illustrate the relationship between the time-to-onset and the outcome. It is therefore reasonable to use the Cox regression model to calculate the incidence rate and the HR for incident cardiotoxicity events in combination therapies compared with ICI therapy alone. A previous study revealed a similar method for estimating the causal relationship between exposure and outcomes.[20] As we can see from Table 3, the crude HR (1.1) of ICI combined with targeted therapy is performed from the incidence rate (4.0 divided by 3.2), demonstrating that ICI combined with targeted therapy had a slightly higher risk compared to ICI therapy. Therefore, we have confirmed that whether the time of follow-up is considered, it might affect the result of the subsequent analysis. Hence, we consider that the use of incidence rate is more accurate than the incidence for analyzing drug-related adverse effects.

ICI therapy-related cardiotoxicity is not commonly reported in Asian populations.[21,22] John et al. reported the efficacy and safety outcomes of Asian patients with lung cancer treated with nivolumab plus ipilimumab combined with chemotherapy. The majority of the adverse effects of immunological cause was rash, alopecia, and followed by endocrine system. In addition to John et al., Lee et al. reported the absence of related cardiovascular irAEs in their study. Moreover, some articles showed that myocarditis was a very rare adverse event in the Taiwanese population.[23,24] In contrast, according to the global database individual case safety reports published by the World Health Organization, myocarditis (41%) is the most common adverse event noted in patients with melanoma, with a mortality rate that in some cases reaches 50%.[25] Our cohort included only one patient with melanoma who did not experience any cardiotoxic irAEs. In addition, we observed heart failure and arrhythmia were more common than myocarditis. The finding is consistent with the results of Waheed et al.[19] The pathophysiology of ICI-related cardiotoxic effects is incompletely understood. In clinical conditions, evidence of myocarditis can often be seen on cardiac magnetic resonance imaging, cardiac PET/CT, or endomyocardial biopsy. Early symptoms suggest a higher risk of arrhythmia and serum cardiac biomarkers such as troponin, creatine kinase-muscle/brain (CK-MB) are elevated.[26,27] Besides, myocarditis is not easily detected because ICI-related heart failure symptoms might have a delayed time-to-onset.[28–30] Therefore, it is important to investigate the relationship between ICI-related various cardiotoxicity and ethnic differences or different types of cancer in larger cohort studies.

Moreover, the present study considered various potential confounding factors, including age, gender, hypertension, cardiovascular diseases, chronic kidney diseases, diabetes mellitus, hyperlipidemia, BMI, smoking status, alcohol consumer, betel nut chewing behavior, combination of other drugs that might induced or aggravate heart failure, and radiation sites. Among those factors, impaired renal function was found to be a distinct risk factor of death, cardiovascular events, and hospitalization.[31] Most experts believe that there are physiological interactions between the heart and kidney. Renal dysfunction can cause sodium and water retention leading to high blood pressure and cardiac stress. In another perspective, impaired cardiac function will reduce cardiac output, and subsequently decrease renal arterial perfusion, increase oxidative stress and vascular calcification, etc, ultimately resulting in renal vascular resistance and impaired renal function.[32] Hyperlipidemia was one of the confounders in this study. A number of studies have revealed that hyperlipidemia leading to atherosclerosis in the blood vessels may directly affect the heart by increasing ischemia or reperfusion injury.[33] Long-term hyperlipidemia may lead to cardiac dysfunction, affect electrophysiological activity, and LV structure and function.[34,35] In addition, a high level of nonfasting triglycerides was reported to increase the risk of heart failure.[36] Another distinct confounder identified in this study was betel nut chewing, which is common in Asian countries, such as Taiwan and India, and is also a risk factor for oral cancer. Betel nut is one of the most broadly used and highly addictive substances worldwide. Furthermore, previous epidemiological studies showed that betel nut usage is associated with an increased risk of cardiovascular diseases.[37–39]

Corticosteroids that are the most prescribed drugs in cancer patients have been routinely used to mitigate immune-related adverse effects of ICI therapy in recent years. Those issues are covered by several guidelines, for example, the National Comprehensive Cancer Network, the European Society of Medical Oncology, etc.[40,41] Do corticosteroids affect the efficacy of ICI therapy? A meta-analysis including 4045 patients treated with corticosteroids for adverse events of ICI showed that no negative effect on overall survival (OS). But, corticosteroids used for supportive care (eg, disease-related symptoms) were negatively impacted both OS and progression-free survival.[42] Corticosteroids might carefully consider in the case of combined ICI with their indications. On the other hand, some reports have indicated that certain non-cardiac medications, such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, might also induce or worsen heart failure.[43] It is therefore necessary to evaluate and adjust for these potential risk factors prior to the administration of ICIs to detect drug-related cardiotoxicity in our study.

This study did not find a significantly higher risk of cardiotoxicity among cancer patients treated with ICI therapy combined with either chemotherapy or targeted therapy after adjusting for betel nut chewing behavior, hyperlipidemia, and concurrent use of other medications, and were consistent with the results of two previous studies.[10,13] On the contrary, few studies reported that dual ICI therapy and combination with other anticancer agents increased the incidence of ICI-related cardiotoxicity.[44–47] There are several possible explanations for this discrepancy. First, logistic regression is commonly used for evaluating the efficiency of drug therapies via estimating the OR or RR in clinical trials. However, after analyzing both aRR and aHR, a significantly higher risk for drug-related cardiotoxicity was not identified in our study. Second, we had initially speculated that the combination treatment of ICIs and chemotherapy (eg, anthracyclines) might increase the risk of cardiotoxicity. Only 1.7% of our patients received anthracyclines, and thus we might not find statistically significant toxic effects. Third, prior evidence revealed that patients treated with targeted therapies, such as bevacizumab and sorafenib might be at an increased risk of developing cardiac adverse events, including cardiac and cerebral ischemia, venous adverse events, and hypertension,[48,49] but <2.0% of our patients received those drugs. According to a relative lower proportion of high-risk cardiotoxicity medications in this cohort, we might not find a significantly higher risk of cardiotoxicity between ICI therapy alone and combination of chemotherapy or targeted therapy in this cohort. Nevertheless, we still recommend that it is careful to evaluate patients receiving high-risk cardiotoxicity medications, such as anthracyclines and human epidermal growth factor receptor-2 inhibitors, to avoid drug-related cardiotoxicity with a combination of ICI therapy.

It is sufficient for statistical analysis of cardiotoxicity even though cardiac toxicity incidence rate is low. Table 3 indicated the cardiac toxicity incidence rate was 4.0 per 100 person-years in ICI with the targeted therapy group (n = 33) and 5.4 per 100 person-years in ICI with the chemotherapy group (n = 59), both are higher than the ICI therapy group (n = 315) of 3.2 per 100 person-years. Therefore, it is obvious that the low cardiac toxicity incidence rate is not due to the unbalanced number of three groups. Although the percentage of cardiotoxicity of ICI plus chemotherapy or targeted therapy was relatively low, our study indicated that Cox regression was a better method compared to logistic regression in analyzing the risk of cardiotoxicity. In addition, we have confirmed that whether the time of follow-up is considered, it might affect the result of the subsequent analysis. We consider that the use of incidence rate is more accurate than the incidence for analyzing drug-related adverse effects.

Our study has some limitations. First, only one single teaching hospital in Taiwan was included in this study. Therefore, patients who might have visited other hospital for medical consultations would have incomplete medical records and might have been excluded in this study. Second, patients with high mortality rates at stage IV diagnosis were followed up for a limited time, and the risk of drug-induced cardiotoxicity might have been low for patients treated with a short duration of anticancer drug therapy in our study. Third, the concurrent use of medications worsening or protecting cardiac function was very challenging to assess. Accordingly, we only selected the most commonly used medications worsening cardiac function, such as NSAIDs and corticosteroids. Potential risk factors of other drug-related cardiovascular events or the beneficial factors of the heart should not be excluded. Finally, the effect of complex drug–drug interactions on the risk of cardiovascular adverse events should not be excluded as well. However, whether the deteriorating or protective effects to cardiac function between concomitant medications is very difficult to evaluate. Besides, cancer treatment strategies are quite complicated. Physicians will change treatment strategies according to the patient's condition. Therefore, certain patients would cross-over treatments in our observation period. Nevertheless, we believe that our results are accurate, and demonstrate that ICI therapy combined with other anticancer drugs does not significantly increase the risk of cardiotoxicity in cancer patients.

In conclusion, our study is the first to report that the combination of ICI with either chemotherapy or targeted therapy does not increase the risk of cardiotoxicity among cancer patients. Nevertheless, it is recommend being careful in patients treated high-risk cardiotoxicity medications to avoid drug-related cardiotoxicity with a combination of ICI therapy. Additionally, the total incidence rate of cardiotoxicity was 3.6 per 100 person-years. We suggest that the incidence rate and the HR are more precise parameters for estimating the risk of drug-related adverse effects in pharmaceutical research.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A183, http://links.lww.com/JCMA/A184, and http://links.lww.com/JCMA/A185.

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