Original Article
Association between immune checkpoint inhibitors and cardiovascular risks: a nationwide self-controlled case series study

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Abstract: Immune checkpoint inhibitors (ICIs) are widely used for cancer treatment but are linked to potential cardiotoxicity. The time-dependent effects of ICIs on cardiovascular outcomes remain unclear. This study explores associations between ICI use and cardiovascular events. This self-controlled case series (SCCS) analyzed cancer patients who received ICIs from January 2019 to December 2020 using the National Health Insurance Research Database (NHIRD). Exposure periods were defined as the duration of ICI prescriptions plus 90 days. Poisson regression estimated incidence rate ratios (IRRs) for heart failure (primary outcome) and arterial events or perimyocarditis (secondary outcomes) during and after ICI exposure compared to baseline. Among 1,146 ICI users, 15 developed heart failure, 33 experienced arterial events, and 11 had perimyocarditis. Cardiovascular events were uncommon but showed elevated risks for heart failure (IRR: 7.73; CI: 2.05-29.14, P<0.01) and perimyocarditis (IRR: 8.25; CI: 1.60-42.50, P = 0.01) within 30 days of ICI exposure. Subgroup analysis identified higher risks in patients aged ≥65, males, and those with diabetes, hypertension, or hyperlipidemia. Furthermore, when focusing on patients who received more than two doses of ICIs or exclusively anti-PD-1 inhibitors, we observed a similarly increased risk of HF within 30 days post-exposure. Collectively, ICI exposure significantly elevates the risk of heart failure and perimyocarditis within 30 days, particularly in older adults and those with preexisting cardiovascular risk factors.

Keywords: Immune checkpoint inhibitors, self-controlled case series, heart failure, perimyocarditis

Introduction

The use of immune checkpoint inhibitors (ICIs), such as PD-1/PD-L1 and CTLA-4 inhibitors, has revolutionized cancer treatment by enhancing T-cell activation [1, 2]. However, inhibiting checkpoints like PD-1 and CTLA-4, ICIs not only promotes anti-tumor responses but also results in unintended immune activation against healthy tissues [3, 4]. This dysregulation may cause a range of immune-related adverse events (irAEs), including dermatologic, endocrine, gastrointestinal, and hepatic toxici-

ties [5, 6]. Although often manageable, some irAEs can be severe or even fatal. To note, ICIs triggered autoimmune reactions in cardiovascular system may cause severe complications such as myocarditis, pericarditis, heart failure (HF), and thromboembolic events [3, 5, 7-9]. Recent studies have highlighted the importance of early detection and management of irAEs to optimize patient outcomes but previous cohort studies examining the relationship between ICIs and cardiovascular complications face several challenges [3, 5, 7-9]. Selection bias is common, as patients receiving ICIs often
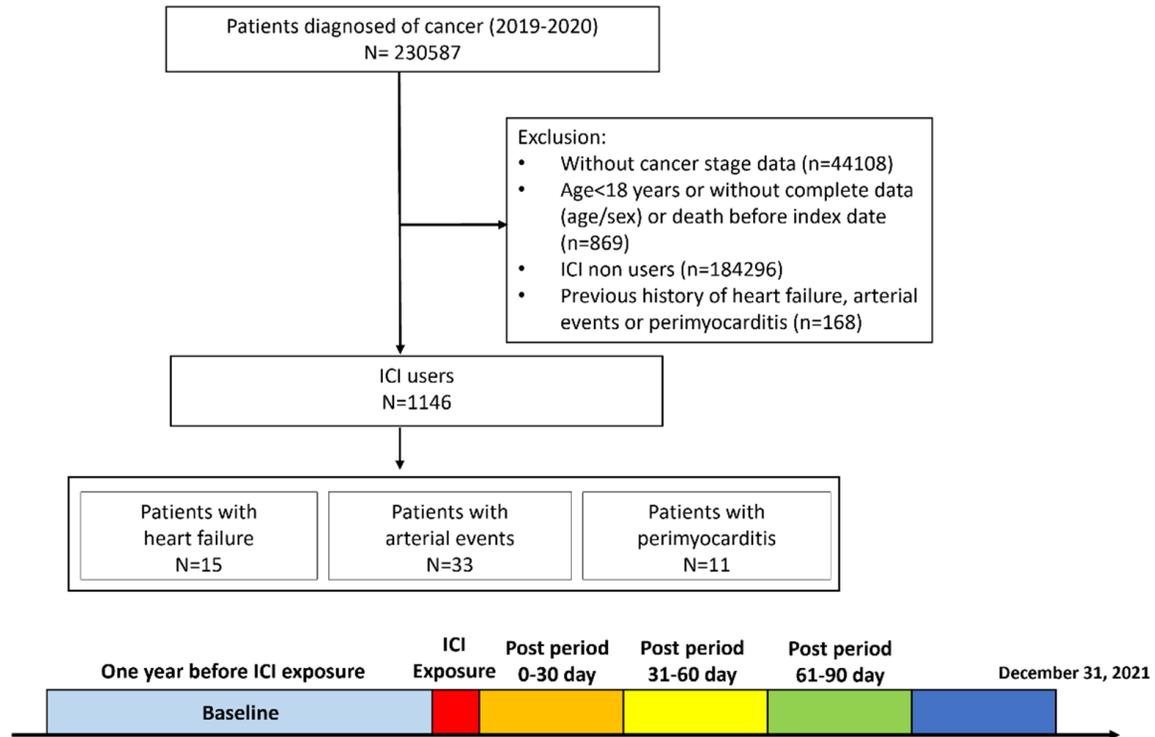
Figure 1. The flowchart of study design.

differ from those not treated, which can confound results [10]. Identifying appropriate control groups is also difficult, as mismatches in baseline characteristics may distort findings. Furthermore, confounding factors such as pre-existing cardiovascular conditions and lifestyle choices complicate data interpretation [2, 10]. Temporal bias may arise from difficulties in accurately timing cardiovascular events in relation to ICI treatment, and incomplete follow-up can skew incidence rates [11]. In contrast, the self-controlled case series (SCCS) analysis offers several advantages [11, 12]. This method compares individuals to themselves, effectively controlling for time-invariant confounders such as genetics and pre-existing conditions. By focusing on within-individual comparisons, SCCS reduces bias related to between-group differences and enables more efficient data use, even with smaller sample sizes [13]. It also directly analyzes incidence rates during exposure periods, making it easier to assess the temporal relationship between ICIs and cardiovascular events [13, 14]. In this study, we aim to investigate the associations between ICI use and cardiovascular outcomes, including HF, arterial events, and perimyocarditis, using

the SCCS approach. Additionally, subgroup analyses will help us evaluate the impact of pre-existing risk factors on ICI-associated cardiovascular complications.

Methods

Patients

Using the Taiwanese National Health Insurance Research Database (NHIRD) and National Cancer Registry, we observed patients diagnosed with cancers between January 2019 and December 2020. As shown in **Figure 1**, patients younger than 18 years old, those with incomplete data, those who died before the index date, those without ICI use, and those with a previous history of heart failure, arterial events, or perimyocarditis were excluded. ICIs included PD-1 inhibitors (nivolumab, pembrolizumab), PD-L1 inhibitors (atezolizumab, avelumab and durvalumab), and CTLA-4 inhibitor (ipilimumab). The database provided details on patients' age, sex, medical history, concurrent medications taken within the past three months, and any treatments or procedures received. The diagnosis codes in NHIRD were identified using the

International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-9 and ICD-10-CM) (Supplementary Table 1). Within the NHIRD, the continuous claim data could be tracked for the same patient. Our institutional review board in National Cheng Kung University Hospital, Tainan, Taiwan approved this study (IRB A-EX-111-003; CV code: 10406-E01), and because it was retrospective, they waived informed consent.

Study design and endpoints

This study employs a SCCS design. SCCS is a type of case-only study where only patients who experience the outcome of interest are analyzed [13, 15]. This approach was selected because, in observational settings, it can be challenging to find appropriate control groups to compare against patients receiving ICIs without introducing significant bias by indication [13, 15]. Bias by indication occurs when clinical differences between exposure groups influence both the treatment received and the outcomes observed, making it difficult to account for in statistical analyses. In contrast to cohort studies that rely on between-individual comparisons, SCCS focuses on within-individual comparisons of event incidence before and after exposure [15, 16]. The index date was set as the first day of ICIs use. The baseline period was defined as one year before the first ICI prescription, and exposure periods included continuous ICI prescriptions and the following 90 days, until reaching the endpoints, death, or end of follow-up (December 31, 2021). The primary result was HF while the secondary outcomes include arterial events and perimyocarditis. Arterial events include acute myocardial infarction and ischemic strokes while perimyocarditis include myocarditis, pericarditis and pericardial effusion.

Statistical analysis

Fixed-effects conditional Poisson regression was used to estimate incidence rate ratios (IRRs) of cardiovascular outcomes during and after ICI exposure, compared to baseline. Multivariable adjustments were not applicable, as the paired- pre-post comparisons in SCCS inherently adjust for time-invariant confounders. A subgroup analysis was performed for patients reaching the primary endpoint of HF to evaluate the impact of ICI exposure in patients with different cardiovascular risk factors. In sensitivity tests, the IRR analysis was performed for patients receiving more than two doses of ICIs (**Table 3**) and separately for those receiving anti-PD-1 inhibitors (**Table 4**) while the IRRs for HF, arterial events and perimyocarditis were assessed using the same time stratification. All analyses of the data were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC).

Results

Baseline characteristics

As shown in **Table 1**, among the included 1,146 ICI users, the majority of patients receiving ICIs in 2020 (47.03%), followed by 2021 (38.74%) and 2019 (14.22%). The mean age of patients is approximately 63.61 years (median age of 64 years) while the majority of patients are male (77.49%). The most common cancer type is lung cancer (46.25%), followed by genitourinary cancers (15.79%) and other types (30.98%). Most patients have advanced stage cancer, with 63.35% in stage 4 and 21.29% in stage 3. In terms of catdiovascular comorbidities, 40.05% of patients had hypertension, 26.88% had diabetes mellitus, and 22.95% had hyperlipidemia. Also, a significant number of patients are on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) (25.57%), beta blockers (21.12%), and statins (18.32%).

Risks of cardiovascular outcomes in patients receiving ICIs

To minimize bias in observational studies, the SCCS approach was selected due to its ability to control for time-invariant confounders. As shown in **Table 2**, among patients receiving ICIs, 15 reached the endpoint of HF, 33 experienced arterial events, and 11 developed perimyocarditis during the study period. Despite the relatively low number of cardiovascular events, there was a significantly increased risk of HF (IRR: 7.73; CI: 2.05-29.14, P<0.01) and perimyocarditis (IRR: 8.25; CI: 1.60-42.50, P = 0.01) within 30 days of ICI exposure, though the IRR became insignificant in the subsequent period. In contrast, the IRR for arterial events was initially insignificant but showed an upward trend during days 31-60 (IRR: 7.23; CI: 0.89-58.79, P = 0.06). During days 61-90, the IRRs

Table 1. The baseline characteristics of patients receiving immune checkpoint inhibitors (ICIs)

	Total N = 1146
Year	Number (%)
2019	163 (14.22)
2020	539 (47.03)
2021	444 (38.74)
Age	
Mean (SD)	63.61 (11.64)
Median (IQR)	64.00 (16.00)
Sex	
Male	888 (77.49)
Female	258 (22.51)
Cancer type	
Gastrointestinal	67 (5.85)
Lung	530 (46.25)
Breast	4 (0.35)
Gynecological	3 (0.26)
Genitourinary	181 (15.79)
Hematologic malignancy	6 (0.52)
Others	355 (30.98)
Stage	
0	10 (0.87)
1	85 (7.42)
2	81 (7.07)
3	244 (21.29)
4	726 (63.35)
Comorbidities	
Coronary artery disease	102 (8.90)
Peripheral artery disease	17 (1.48)
Hypertension	459 (40.05)
Diabetes mellitus	308 (26.88)
Hyperlipidemia	263 (22.95)
Valve diseases	16 (1.40)
COPD	184 (16.06)
Asthma	44 (3.84)
CKD/ESRD	137 (11.95)
Medication	
Anti-platelet agents	106 (9.25)
Anti-coagulants	32 (2.79)
Statins	210 (18.32)
ACEIs/ARBs	293 (25.57)
Beta blockers	242 (21.12)

ACEIs/ARBs = angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; ESRD = end-stage renal disease; IQR = interquartile range; SD = standard deviation.

for all three cardiovascular endpoints showed no significant changes.

Subgroup analysis focusing on patients developing HF

To evaluate the effects of pre-existing cardiovascular risk factors, we performed a subgroup analysis (**Figure 2**). To note, patients aged 65 or older (IRR: 6.87, CI: 1.39-34.04, P = 0.02), male patients (IRR: 8.25, CI: 1.60-42.50, P< 0.01) and those with cardiovascular risk factors such as diabetes (IRR: 20.6, CI: 4.16-102.13, P<0.01), hypertension (IRR: 30.92, CI: 5.17-185.04, P <0.01) or hyperlipidemia (IRR: 13.74, CI: 2.30-82.24, P<0.01) had higher risks for the subsequent HF.

Sensitivity tests

To validate our findings, we performed an IRR analysis of cardiovascular outcomes in patients receiving more than two doses of ICIs, as shown in **Table 3**. We observed a significantly increased risk of HF (IRR: 6.87; CI: 1.39-34.04, P = 0.02) within 30 days of ICI exposure, while the IRRs for arterial events were not significant during the same period. Beyond 30 days, the IRR for HF also showed no significant changes. Furthermore, given that the majority of the studied patients received anti-PD-1 inhibitors, we focused on the IRR of cardiovascular outcomes in this subgroup (**Table 4**). Notably, within 30 days of exposure to anti-PD-1 inhibitors, patients had a significantly increased risk of HF (IRR: 8.83; CI: 2.28-34.16, P<0.01) and perimyocarditis (IRR: 8.25; CI: 1.60-42.50, P = 0.01), whereas the IRRs became insignificant in the subsequent period.

Discussion

Among 1,146 ICI users, the SCCS analysis revealed a significantly increased risk of HF and perimyocarditis within 30 days of ICI exposure. In the subgroup analysis focusing on HF, patients aged 65 or older, male patients, and those with pre-existing conditions like diabetes, hypertension, or hyperlipidemia had notably higher risks for HF following ICI treatment. Also, as focusing on patients receiving more than two doses of ICIs or receiving only anti-PD-1 inhibitors, we observed similar findings of an increasing risk of HF within 30 days post

Table 2. The incidence rate ratio (IRR) of cardiovascular outcomes in patients receiving *i*mmune checkpoint inhibitors *(ICIs)*

	Total N = 1146	0-30 days		31-60 days		61-90 days	
		IRR (95% CI)	*p* value	IRR (95% CI)	*p* value	IRR (95% CI)	*p* value
Primary outcome							
Heart failure	15 (1.31)	7.73 (2.05-29.14)	<0.01	1.03 (0.21-5.12)	0.97	0.34 (0.04-3.31)	0.36
Secondary outcome							
Arterial events*	33 (2.88)	1.03 (0.14-7.68)	0.98	7.23 (0.89-58.79)	0.06	5.17 (0.6-44.22)	0.13
Perimyocarditis**	11 (0.96)	8.25 (1.60-42.50)	0.01	1.55 (0.26-9.28)	0.63	0.52 (0.05-5.70)	0.59

CI = confidence intervals; IRR = incidence rate ratio. *Arterial events including acute myocardial infarction and ischemic stroke. **Perimyocarditis including myocarditis, pericarditis and pericardial effusion.

Table 3. The incidence rate ratio (IRR) of cardiovascular outcomes in patients receiving more than two doses of *i*mmune checkpoint inhibitors *(ICIs)*

	0-30 days		31-60 days		61-90 days	
	IRR (95% CI)	*p* value	IRR (95% CI)	*p* value	IRR (95% CI)	*p* value
Primary outcome						
Heart failure	6.87 (1.39-34.04)	0.02	1.55 (0.26-9.28)	0.63	0.52 (0.05-5.70)	0.59
Secondary outcome						
Arterial events*	1.29 (0.17-9.71)	0.81	4.13 (0.46-36.98)	0.20	3.10 (0.32-29.80)	0.33
Perimyocarditis**	4.12 (0.48-35.29)	0.20	2.07 (0.19-22.79)	0.55	1.03 (0.06-16.52)	0.98

CI = confidence intervals; IRR = incidence rate ratio. *Arterial events including acute myocardial infarction and ischemic stroke. **Perimyocarditis including myocarditis, pericarditis and pericardial effusion.

Table 4. The incidence rate ratio (IRR) of cardiovascular outcomes in patients receiving anti-PD-1 inhibitors

	0-30 days		31-60 days		61-90 days	
	IRR (95% CI)	*p* value	IRR (95% CI)	*p* value	IRR (95% CI)	*p* value
Primary outcome						
Heart failure	8.83 (2.28-34.16)	<0.01	1.03 (0.21-5.12)	0.97	0.34 (0.04-3.31)	0.36
Secondary outcome						
Arterial events*	1.03 (0.14-7.68)	0.98	7.23 (0.89-58.79)	0.06	4.13 (0.46-36.98)	0.20
Perimyocarditis**	8.25 (1.60-42.50)	0.01	1.55 (0.26-9.28)	0.63	0.52 (0.05-5.70)	0.59

Anti-PD-1 inhibitors include nivolumab, pembrolizumab. CI = confidence intervals; IRR = incidence rate ratio. *Arterial events including acute myocardial infarction and ischemic stroke. **Perimyocarditis including myocarditis, pericarditis and pericardial effusion.

exposure. Our findings highlighted that early recognition and prompt management of cardiovascular events are essential for optimizing patient outcomes and minimizing risks during immunotherapy. Pre-existing cardiovascular risk factors are prevalent and should be regarded as risk factors to increase the likelihood of developing cardiovascular complications (**Figure 3**).

Previous studies investigating the association between ICIs and cardiovascular complications have highlighted various immune-related adverse events [13, 15]. However, they often face challenges such as small sample sizes, selection bias, and inconsistent reporting [4, 5, 8]. In a meta-analysis of 48 studies [9], Malaty et al. reported that while ICI-mediated cardiovascular toxicities are rare, they can be potentially fatal. The incidence of myocarditis in ICI-treated patients has been reported to range from 0.06% to 1.14%, though actual rates may be higher due to underreporting and misdiagnosis [17]. Among various cardiovascular complications, pericarditis, though less common, has also been reported [18]. Similarly, we

Heart failure

	IRR (95% CI)	p-value
Age		
<65yrs	10.31 (0.93-113.66)	0.06
≥65yrs	6.87 (1.39-34.04)	0.02
Sex		
Male	8.25 (1.60-42.50)	<0.01
Female	6.87 (0.71-66.05)	0.10
Diabetes mellitus	20.61 (4.16-102.13)	<0.01
Hypertension	30.92 (5.17-185.04)	<0.01
Hyperlipidemia	13.74 (2.30-82.24)	<0.01
Total	7.73 (2.05-29.14)	<0.01
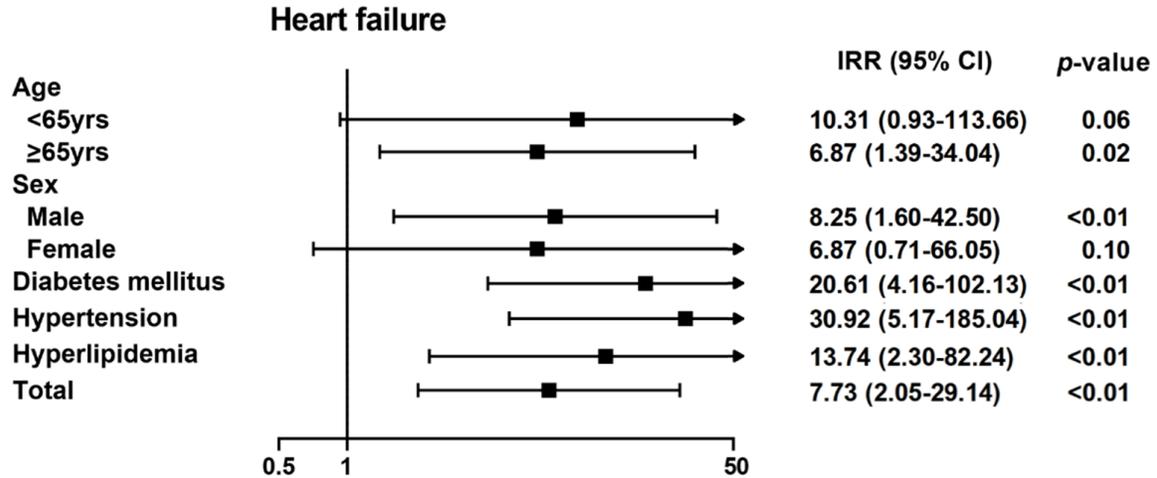
Figure 2. Subgroup analysis focusing on patients developing heart failure during 0-30 days post immune checkpoint inhibitors.
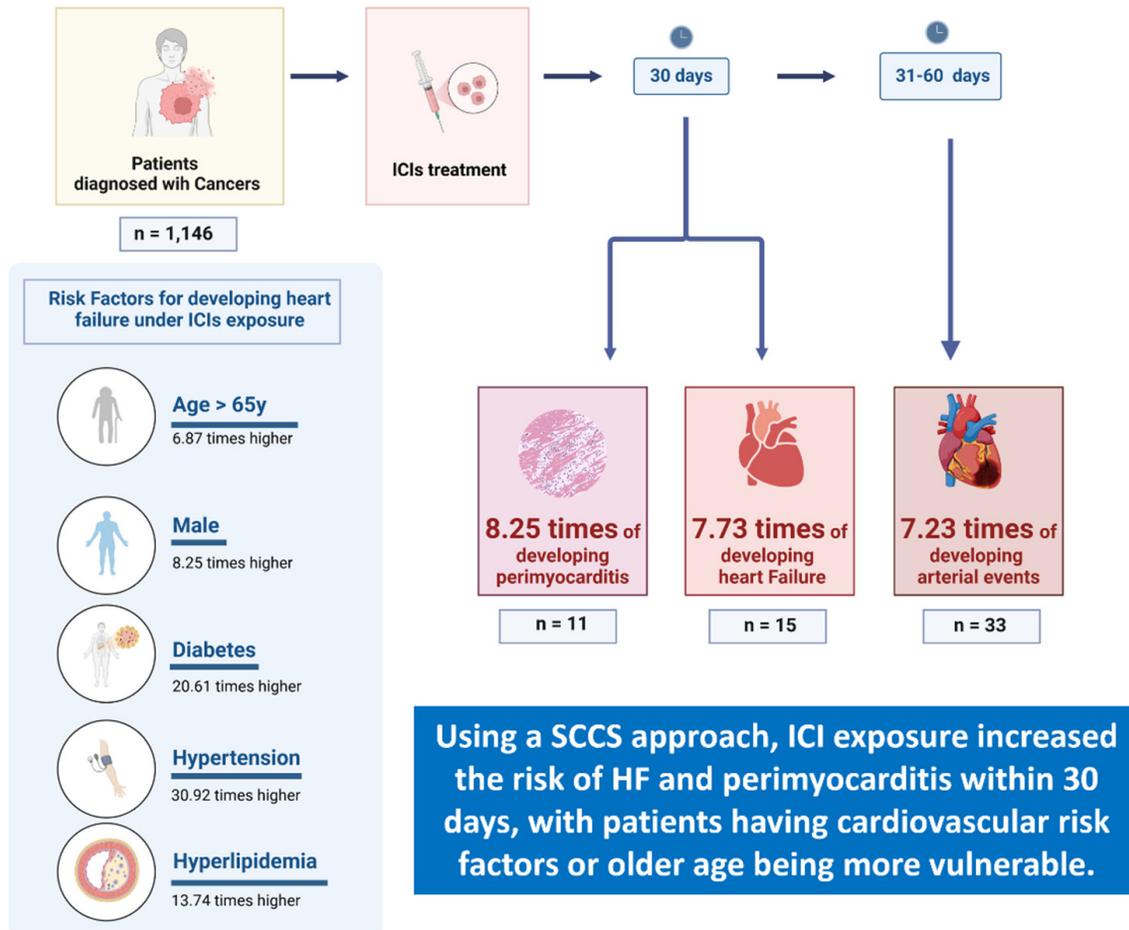
Figure 3. Using a nationwide self-controlled case series (SCCS) approach, among 1,146 ICI users the exposure of immune checkpoint inhibitors (ICIs) was associated with increasing incodences of cardiovascular complications within 30 days.

observed a significantly increased risk of HF and perimyocarditis within 30 days of ICI exposure, particularly among patients receiving anti-PD-1 inhibitors. While we did not find significant changes in the incidence of arterial events, such as myocardial infarction and ischemic stroke, following ICI exposure, Drobni et al. reported an overall increase in cardiovascular events after ICI initiation, potentially driven by accelerated atherosclerosis progression [19]. Notably, while some cohort studies and case reports have documented an elevated risk of cardiovascular complications in ICI users, particularly within the first few weeks of treatment [5, 8, 20], none have provided a detailed analysis of risk variations over different post-exposure periods. Our findings reinforce this observation, demonstrating a nearly 7-fold increase in HF risk (IRR: 6.87) within 30 days and an even greater risk (IRR: 8.83) among anti-PD-1 users.

Although previous studies tried to investigate the risk of cardiovascular complications in ICI users, these studies often struggle with confounding factors such as pre-existing cardiovascular diseases and differences in baseline characteristics between patients receiving ICIs and those not exposed [3, 5, 8, 20]. Additionally, many of these studies are limited by their observational nature, where control groups may not be adequately matched [5, 20]. SCCS studies inherently control for time-invariant confounders by comparing different time periods within the same individual [21-23]. Unlike traditional observational studies, SCCS eliminates confounding factors such as sex or genetics without requiring additional adjustments like Propensity Score Matching (PSM) [23, 24]. This makes SCCS particularly useful in pharmacoepidemiology, where within-individual comparisons assess exposure risks without the need for extensive matching [15, 16]. Given that we only followed up those patients for 90 days after ICI exposure, the effect of time-varying confounding factors was minimized.

Using SCCS, Chan et al. investigated the association between ICIs and myocardial infarction among 3,684 ICI users in Hong Kong [14]. A significantly increased risk was observed within the first 90 days of ICI exposure (IRR 3.59) while no significant association was found beyond 90 days or after ICI treatment [14].

Similar to our findings, SCCS analysis also revealed a significantly increased risk of HF (IRR: 7.73) and perimyocarditis (IRR: 8.25) within 30 days of ICI exposure, while these risks became insignificant afterward. Additionally, in subgroup analysis, we found that patients with pre-existing cardiovascular risk factors, such as older age, diabetes, hypertension, and hyperlipidemia, were prone to have an higher risk of heart failure following ICI treatment. Our findings suggest that clinicians should closely monitor the cardiovascular health of ICI-treated patients, particularly those with known risk factors. Early detection and management of cardiovascular complications may improve outcomes and reduce the likelihood of severe adverse events. Moreover, these results highlight the importance of personalized treatment strategies and cardiovascular screening during and after ICI therapy.

Limitations

There are still some limitations of this study. First, SCCS is generally better suited for assessing short-term outcomes, as the design focuses on defined exposure windows [21]. Thus, the long-term effect of ICI uses on cardiotoxicity remains uncertain. Second, although SCCS adjusts for time-invariant confounders, it assumes a constant risk and presents the risk of misclassification. Once a patient is diagnosed with cancer and begins therapy, clinical monitoring intensifies compared to the pre-diagnosis period, which may lead to a higher rate of detection for asymptomatic or subclinical conditions. Third, for effective analysis there must be enough events occurring in the study population, which can limit its applicability in rare outcomes [15, 16]. Forth, diagnostic accuracy for myocarditis in individual patients was not accessible. However, in the study by Chang and colleagues, using the same nationwide cohort, they conducted a validation study comparing their findings to medical records of hospitalized patients with the ICD-9-CM code 422 (myocarditis). Notably, the positive predictive value was 96.5%. Also, the results may have been affected by the exclusion of those with a previous history of heart failure, arterial events, or perimyocarditis. Fifth, given that some patients received repeated ICI treatments, we further examined the distribution of treatment numbers. As shown in Supplementary Table 2, the

majority of patients underwent either 4 (28.1%) or 5 (19.5%) treatments within the 90-day window. However, whether receiving more treatments increases the risk of adverse cardiac events or whether treatment discontinuation was due to cardiac toxicity or other factors requires further investigation. Additionally, cancer-related deaths could act as a competing risk when evaluating cardiovascular outcomes. Supplementary Table 3 presents data on deaths occurring during ICI exposure within 90 days of treatment initiation. Among 258 patients (22.5% of the cohort) who died, deaths were distributed relatively evenly over the 90-day period, with the highest proportion (36%) occurring between days 31 and 60. While Fine-Gray models may not adequately account for death as a competing risk in SCCS analyses, investigating the causes of death could provide valuable insights into their relationship with ICI exposure. Last, the exact mechanisms behind these complications remain under investigation while hypotheses suggest that ICIs may trigger autoimmune-mediated damage to cardiovascular tissues, leading to myocarditis, HF, and vascular events [2]. Despite these limitations, the study utilized a robust and accurate database with good data completeness. However, further studies are needed to validate these findings in other populations and assess the long-term cardiovascular risks of ICIs.

Conclusions

The study found that ICI exposure significantly increased the risk of HF and perimyocarditis within 30 days, with patients having cardiovascular risk factors or older age being more vulnerable. Our findings highlight the need for heightened cardiovascular monitoring in cancer patients undergoing ICIs, particularly within the first 30 days of treatment. Identifying patients with pre-existing cardiovascular risk factors can guide more personalized risk mitigation strategies to prevent or manage HF and perimyocarditis, ultimately improving patient safety and treatment outcomes during cancer therapy.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. ICD-9 and ICD-10 codes

Disease	ICD-9 Codes	ICD-10 Codes
Outcome		
AMI	410	I21, I22, I23
CHF	428.xx, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	I11.0, I13.0, I13.2, I42.0, I42.1, I42.2, I42.3, I42.4, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9
Cardiomyopathy	425	I42
Ischemic stroke (including TIA)	433, 434, 435, 436	I63, I65, I66, I67.89, I67.84, G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2
Myocarditis	422, 429.0	I41, I40, I51.4, I51.5
Pericarditis	420	I30, I32
Comorbidities		
Coronary artery disease	410, 411, 412, 413, 414	I20, I21, I22, I24, I25
Peripheral artery disease	440, 443, 444, 447.8, 447.9	I70.2-I70.9, I71, I73.9, I74.2, I74.3, I74.4, I74.5, I77.89, I77.9
Hypertension	401, 402, 403, 404, 405	I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.2, I13.11, I15, N26.2
Diabetes mellitus	250	E08, E09, E11, E13
Hyperlipidemia	272	E78
Valve disorders	394-397, 424.0, 424.1, 424.2, 424.3	I05, I06, I07, I08, I09, I34-I37
Chronic obstructive lung disease	491, 492, 494, 495, 496	J41, J42, J43, J44, J47, J67
Asthma	493	J45
Atrial fibrillation	427.31, 427.32	I48
Chronic kidney disease	580-589, 403, 404, 585, V45.1, V56	I12, I13, N02, N03, N04, N05, N06, N07, N08, N11, N14, N17, N18, N19, N29, O10.2, O10.3, Q61, Z49, Z99.2
ESRD	585.6	N18.6; Z99.2

Supplementary Table 2. The number of immune checkpoint inhibitor (ICI) treatments received by the studied patients within the 90-day window

Times of ICIs	Number	%
1	178	15.5
2	129	11.2
3	147	12.8
4	322	28.1
5	224	19.5
>5	146	12.7

Supplementary Table 3. The duration after immune checkpoint inhibitor exposure among 258 patients who died within the 90-day window

Day	Number	%
0-30	77	29.8
31-60	94	36.4
61-90	87	33.7