Cardiovascular Outcomes and Hospitalizations in Asian Patients Receiving Immune Checkpoint Inhibitors: A Population-based Study

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Abstract: Immune checkpoint inhibitors (ICI) have known associations with cardiotoxicity. However, a representative quantification of the adverse cardiovascular events and cardiovascular attendances amongst Asian users of ICI has been lacking. This retrospective cohort study identified all ICI users in Hong Kong, China, between 2013 and 2021. All patients were followed up until the end of 2021 for the primary outcome of major adverse cardiovascular event (MACE;

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a composite of cardiovascular mortality, myocardial infarction, heart failure, and stroke). Patients with prior diagnosis of any component of MACE were excluded from all MACE analyses. In total, 4324 patients were analyzed (2905 (67.2%) males; median age 63.5 years old (interquartile range 55.4-70.7 years old); median follow-up 1.0 year (interquartile range 0.4-2.3 years)), of whom 153 were excluded from MACE analyses due to prior events. MACE occurred in 116 (2.8%) with an incidence rate (IR) of 1.7 [95% confidence interval: 1.4, 2.0] events per 100 patient-years; IR was higher within the first year of follow-up (2.9 [2.3, 3.5] events per 100 patient-years). Cardiovascular hospitalization(s) occurred in 188 (4.4%) with 254 episodes (0.5% of all episodes) and 1555 days of hospitalization (1.3% of all hospitalized days), for whom the IR of cardiovascular hospitalization was 5.6 [4.6, 6.9] episodes per 100 person-years with 52.9 [39.8, 70.3] days' stay per 100 person-years. Amongst Asian users of ICI, MACE was uncommon, and a small proportion of hospitalizations were cardiovascular in nature. Most MACE and cardiovascular hospitalizations occurred during the first year after initiating ICI. (Curr Probl Cardiol 2023;48:101380.)

Introduction

Whilst immune checkpoint inhibitors (ICI) have become an established treatment option for a number of malignancies,[1] such as those of lung, head and neck, skin, and other organs, recent years have seen an increasing understanding of ICI-related adverse effects, such as hepatotoxicity, colitis, and cardiotoxicity.[2-4] ICI is associated with increased risks of myocarditis, heart failure (HF), and myocardial infarction (MI), most of which are mechanistically inflammatory: cardio-immune crosstalk disruptions and T-cell and macrophage mediated response to cardiac antigens, which may be direct results of immune checkpoint inhibition, lead to autoantibody-independent processes including inflammatory cell infiltration and myocardial fibrosis, alongside other processes such as IgG deposition and loss of programmed cell death ligand 1 -dependent cardioprotection.[5,6]

Despite many reports of ICI-related cardiotoxicity, studies focusing on the effect of ICI on cardiovascular hospitalization have been scarce. Additionally, despite some studies having explored ICI-related adverse events in Asian cohorts,[7] a representative quantification of cardiovascular risks amongst Asian patients treated with ICI remains lacking. Therefore, we aimed to quantify the burden of cardiovascular hospitalizations and the risk of adverse cardiovascular events amongst Asian users of ICI.

Methods

This retrospective cohort study was approved by the Joint Chinese University of Hong Kong– New Territories East Cluster Clinical Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology guideline. Requirement for individual patient consent was waived as only deidentified data was used. All underlying data are available upon reasonable request to the corresponding authors.

Source of Data

Data were extracted from the Clinical Data Analysis and Reporting System (CDARS), a population-based, administrative electronic medical records system in Hong Kong. CDARS records all diagnostic, procedural and prescription records of patients attending public healthcare institutions in Hong Kong, which serve an estimated 90% of the population.[8] Diagnoses were encoded by *International Classification of Diseases, Ninth Revision* (ICD-9) codes (Supplementary Table 1) regardless of the time of data entry, as ICD-10 has not been implemented in CDARS to date. Mortality data and death causes were obtained from the linked Hong Kong Death Registry, a governmental registry of all Hong Kong citizens' death records; causes of death were encoded by ICD-9 or ICD-10 codes (Supplementary Table 2). Both CDARS and the Hong Kong Death Registry have been used extensively in prior studies and shown to have good coding accuracy and data completeness.[9-13]

Patients, Follow-up, and Outcome

All patients receiving any ICI in Hong Kong between January 1, 2013 and December 31, 2021 were identified. ICI included PD-1 inhibitors (pembrolizumab or nivolumab), programmed cell death ligand 1 inhibitors (atezolizumab, avelumab, or durvalumab), and CTLA4 inhibitor

(ipilimumab); no other ICI were available in Hong Kong during the study period. There were no exclusion criteria for estimating cardiovascular hospitalizations. Patients with prior MI, stroke, or HF were excluded when analyzing the primary outcome, which was major adverse cardiovascular event (MACE), defined as the first occurrence of MI, stroke, HF, or cardiovascular mortality. All patients were followed up until December 31, 2021.

Data Collected

The total number of hospitalization episodes with their respective length of stay (LOS) during the follow-up period was recorded for each patient. Specifically, the total number of cardiovascular hospitalizations, as determined by ICD-9 diagnostic (Supplementary Table 1) and procedural (Supplementary Table 3) codes, was recorded. Overnight hospitalizations were recorded. Baseline variables recorded are detailed in the Supplementary Methods.

Statistical Analysis

Continuous variables were expressed as median with interquartile range (IQR). The Incidence rate (IR) of MACE was estimated. Kaplan-Meier curves were used to visualize the cumulative incidence of MACE over the study period. The 6-month, 1-year, 1.5-year, and 2-year risks of MACE were estimated using life tables. Similar to above, the IR of MACE within the first year of follow-up were also calculated specifically, and a sensitivity analysis was performed in which the IR of MACE was estimated only for patients with at least 1 year of follow-up.

IR of hospitalizations and annualized LOS were estimated with respective confidence intervals (CI) using negative binomial regression with follow-up duration as the exposure variable. As many patients did not have overnight or cardiovascular hospitalizations, the corresponding IR was estimated for patients who had such events using zero-inflated negative binomial regression with constant inflation. Hospitalization-related costs were estimated by multiplying the estimated LOS with the latest per-day cost of in-patient hospital stay (HKD5100, corresponding to €637.5 with a conversion factor of 0.125 at the time of writing) published by the Hong Kong Hospital Authority in 2020.[14] To account for potential changes in IR over time, the IR of hospitalizations within the first year of follow-up were calculated specifically. For similar reasons, a sensitivity

analysis was performed with analyses restricted to patients with at least 1 year of follow-up.

Two-sided $P < 0.05$ were considered statistically significant. All statistical analyses were performed on Stata v 16.1 (StataCorp LLC, College Station, TX).

Results

In total, 4324 patients were identified and included in the analysis (2905 (67.2%) males; median age 63.5 years old, IQR 55.4-70.7 years old). Most patients received a PD-1 inhibitor (3527 patients, 81.6%), and 59.4% (2567 patients) had chemotherapy use at baseline. Half had lung cancer (2179 patients, 50.4%). Hypertension was documented in 1993 patients (46.1%), dyslipidaemia in 1227 (28.4%), and diabetes mellitus in 793 (18.3%); 153 patients had prior diagnosis of stroke, MI, or HF, and were therefore excluded from all MACE analyses. The baseline characteristics of the study cohort were summarized in Table 1.

Major Adverse Cardiovascular Event

Amongst the 4171 patients included in the MACE analysis, MACE occurred in 116 patients (2.8%) over a median follow-up duration of 1.0 year (IQR 0.4-2.3 years), of which 18 (18.1% of those with MACE; 0.4% of all patients) had cardiovascular mortality, 34 (29.3% of those with MACE; 0.8% of all patients) had MI, 15 (12.9% of those with MACE; 0.4% of all patients) had HF, and 55 (47.4% of those with MACE; 1.3% of all patients) had stroke; more than one component of MACE occurred concomitantly in 9 patients (7.8% of those with MACE; 0.2% of all patients). Patients who had MACE had higher rates of cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidaemia, and ischaemic heart disease, and used more cardiovascular and antidiabetic medications (Supplementary Table 4).

Among the 116 patients who had MACE, 90 (77.6%) had MACE within the first year, with a median time-to-event of 0.5 year (IQR 0.2-0.9 year). This early clustering of events was also demonstrated by the Kaplan-Meier curve (Fig 1). The 6-month risk of MACE was estimated to be 1.7% [95% CI: 1.4%, 2.2%], the 1-year risk 2.8% [2.3%, 3.5%], the 1.5-year risk 3.2% [2.6%, 4.0%], and the 2-year risk 4.3% [3.6%, 5.3%]. Concordantly, the IR of MACE within the first year was 2.9 [2.3, 3.5] events per 100 patient-years, with a lower overall IR of 1.7 [1.4, 2.0] events per 100 patient-years throughout the study period. Sensitivity analysis of patients with at least 1 year of follow-up ($N = 2048$) also yielded a

TABLE 1. Baseline characteristics of included patients

	All patients	Patients with cardiovascular hospitalization(s)	Patients without cardiovascular hospitalization(s)
Number of patients, *N*	4324	188	4136
Type of immune checkpoint inhibitor			
Anti-PD-1 user, *N* (%)	3527 (81.6)	160 (85.1)	3367 (81.4)
Anti-PD-L1 user, *N* (%)	873 (20.2)	35 (18.6)	838 (20.3)
Anti-CTLA4 user, *N* (%)	322 (7.5)	16 (8.5)	306 (7.4)
Type of cancer			
Lung cancer, *N* (%)	2005 (46.4)	103 (54.8)	1902 (46.0)
Head and neck cancer, *N* (%)	154 (3.6)	3 (1.6)	151 (3.7)
Nasopharyngeal cancer, *N* (%)	76 (1.8)	1 (0.5)	75 (1.8)
Breast cancer, *N* (%)	138 (3.2)*	6 (3.2)	132 (3.2)
Colorectal cancer, *N* (%)	102 (2.4)	5 (2.7)	97 (2.4)
Liver cancer, *N* (%)	540 (12.5)	22 (11.7)	518 (12.5)
Stomach cancer, *N* (%)	97 (2.2)	2 (1.1)	95 (2.3)
Melanoma, *N* (%)	109 (2.5)	1 (0.5)	108 (2.6)
Renal cell carcinoma, *N* (%)	182 (4.2)	13 (6.9)	169 (4.1)
Esophageal cancer, *N* (%)	46 (1.1)	0 (0)	46 (1.1)
Cervical cancer, *N* (%)	26 (0.6)	1 (0.5)	25 (0.6)
Lymphoma, *N* (%)	181 (4.2)	7 (3.7)	174 (4.2)
Leukaemia, *N* (%)	43 (1.0)	0 (0)	43 (1.0)
Plasma cell dyscrasia, *N* (%)	8 (0.2)	0 (0)	8 (0.2)
Demographics			
Male, *N* (%)	2905 (67.2)	127 (67.6)	2778 (67.2)
Age, y	63.5 [55.4-70.7]	67.7 [58.7-75.9]	63.4 [55.2-70.5]
Comorbid conditions			
Hypertension, *N* (%)	1993 (46.1)	109 (58.0)	1884 (45.6)
Ischaemic heart disease, *N* (%)	201 (4.7)	28 (14.9)	173 (4.2)
Myocardial infarction, *N* (%)	46 (1.1)	6 (3.2)	40 (1.0)
Heart failure, *N* (%)	52 (1.2)	10 (5.3)	42 (1.0)
Atrial fibrillation, *N* (%)	97 (2.2)	12 (6.4)	85 (2.1)
Diabetes mellitus, *N* (%)	793 (18.3)	40 (21.3)	753 (18.2)
Dyslipidaemia, *N* (%)	1227 (28.4)	78 (41.5)	1149 (27.8)
Chronic kidney disease, *N* (%)	39 (0.9)	2 (1.1)	37 (0.9)
Stroke, *N* (%)	76 (1.8)	6 (3.2)	70 (1.7)
Peripheral arterial disease, *N* (%)	7 (0.2)	0 (0)	7 (0.2)
Use of other medications			
ACEI/ARB user, *N* (%)	984 (22.8)	64 (34.0)	920 (22.2)
Metformin user, *N* (%)	594 (13.7)	34 (18.1)	560 (13.5)
Sulfonylurea user, *N* (%)	380 (8.8)	19 (10.1)	361 (8.7)
Insulin user, *N* (%)	370 (8.6)	14 (7.5)	356 (8.6)
DPP4 inhibitor user, *N* (%)	185 (4.3)	12 (6.4)	173 (4.2)
Beta-blocker user, *N* (%)	974 (22.5)	65 (34.6)	909 (22.0)
Statin user, *N* (%)	1144 (26.5)	76 (40.4)	1068 (25.8)
Dihydropyridine CCB user, *N* (%)	1576 (36.5)	85 (45.2)	1491 (36.1)
Chemotherapy user, *N* (%)	2567 (59.4)	99 (52.7)	2468 (59.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CTLA4, cytotoxic T-lymphocyte associated protein 4; DPP4, dipeptidyl peptidase 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.
*9.7% of female patients.

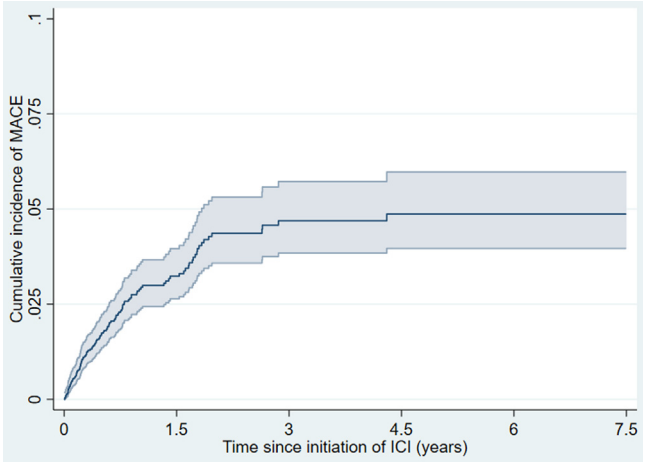

FIG 1. Kaplan-Meier curve showing the cumulative incidence of major adverse cardiovascular event (MACE). ICI, immune checkpoint inhibitor.

lower IR of MACE, which was estimated to be 0.9 [0.7, 1.2] events per 100 person-years.

Hospitalization and Costs

Over a median follow-up duration of 1.0 year (IQR 0.4-2.3 years), 50,578 hospitalization episodes were observed with 123,544 days of hospitalization. Of these, 8752 (17.3%) episodes were overnight hospitalizations, accounting for 81,718 days of hospitalization (66.1% of all hospitalized days). The observed hospitalizations incurred a total cost of €78,759,300, with an annualized per-patient cost of €31,176 [€30,116, €32,274] per patient-year; overnight hospitalizations incurred a total cost of €52,095,225 (66.1% of total hospitalization cost), with an annualized per-patient cost of €36,313 [€34,557, €38,158] per patient-year for those who had overnight hospitalizations.

In total, 188 patients (4.4%) had cardiovascular hospitalization(s), with 254 episodes (0.5% of all episodes) and 1555 days (1.3% of all hospitalized days) of cardiovascular hospitalization; 177 of these episodes (69.7% of cardiovascular hospitalization episodes and 2.0% of all overnight episodes) were overnight hospitalizations, accounting for 1478 days of hospitalization (95.0% of all the days of cardiovascular hospitalization and 1.8% of all the days of overnight hospitalization). Those who had cardiovascular hospitalizations generally had more cardiovascular risk factors, such as hypertension, diabetes mellitus, and

TABLE 2. Incidence rates of hospitalization throughout the study period

	Proportion of patients with event (*N*, %)	Incidence rate [95% CI], episodes per 100 person-y	Annualized LOS [95% CI], d per 100 person-
All admissions	4143 (95.8)	1166.6 [1132.0, 1202.3]	4557.0 [4381.9, 4739.0]
All overnight admissions*	2931 (67.8)	309.6 [292.9, 327.3]	4608.2 [4338.6, 4894.6]
Cardiovascular admissions*	188 (4.4)	5.6 [4.6, 6.9]	52.9 [39.8, 70.3]
Overnight cardiovascular admissions*	142 (3.3)	4.0 [3.1, 5.0]	742.1 [430.3, 1279.7]

CI, confidence interval; LOS, length of stay.
*Estimates calculated for patients with event using zero-inflated negative binomial regression.

dyslipidaemia, and used more cardiovascular or antidiabetic medications; a higher proportion of these patients had lung cancer than those who did not have any cardiovascular hospitalization (Table 1). For those who had cardiovascular hospitalizations, the IR of cardiovascular hospitalization was estimated to be 5.6 [4.6, 6.9] episodes per 100 person-years, with an annualized LOS of 52.9 [39.8, 70.3] days per 100 person-years (Table 2). Overall, the observed cardiovascular hospitalizations incurred a total cost of €991,313 (1.3% of total hospitalization cost), with an annualized per-patient cost of €1614 [€92, €28,257] per patient-year for those with cardiovascular hospitalizations; overnight cardiovascular hospitalizations incurred a total cost of €942,225 (1.2% of total hospitalization cost), with an annualized per-patient cost of €9195 [€6700, €12,620] per person-year for those with overnight cardiovascular hospitalizations.

During the first year of follow-up, higher rates of cardiovascular admissions were observed for those who had cardiovascular hospitalizations, with an estimated 27.7 [0.8, 923.0] episodes per 100 person-years and 253.1 [14.4, 4432.5] days of hospitalization per 100 person-years; similar trends were observed for overnight cardiovascular hospitalizations (Table 3). Similar to the overall analysis, cardiovascular hospitalizations accounted for 0.5% of all hospitalization episodes (199 of 39,623 episodes) and 1.3% of all days of hospitalization (1152 of 99,795 days) during the first year of follow-up; overnight cardiovascular hospitalizations accounted for 69.7% of all cardiovascular hospitalization episodes (140 of 199 episodes), 1.9% of all overnight hospitalization episodes (140 of 67364 episodes), 94.9% of all days of cardiovascular hospitalization (1093 of 1152 days), and 1.6% of all days of overnight hospitalization (1093 of 67,364 days) during the first year of follow-up.

TABLE 3. Incidence rates of hospitalization within the first year of follow-up

	Proportion of patients with event (*N*, %)	Incidence rate [95% CI], episodes per 100 person-y	Annualized LOS [95% CI], d per 100 person-y
All admissions	4142 (95.8)	1388.6 [1358.3, 1419.6]	4890.4 [4724.1, 5062.6]
All overnight admissions*	2693 (62.3)	341.0 [312.0, 372.6]	5696.2 [5420.7, 5985.6]
Cardiovascular admissions*	149 (3.5)	27.7 [0.8, 923.0]	253.1 [14.4, 4432.5]
Overnight cardiovascular admissions*	112 (2.6)	5.0 [4.0, 6.3]	1442.4 [1051.0, 1979.6]

CI, confidence interval; LOS, length of stay.
*Estimates calculated for patients with event using zero-inflated negative binomial regression.

Sensitivity analysis of only patients with at least 1 year of follow-up included 2116 patients. In agreement with the early clustering of attendances as aforementioned, lower IR of hospitalization and annualized LOS were observed for all types of hospitalizations (Supplementary Table 5) than the main analyses above. Notwithstanding this, the IR of cardiovascular hospitalizations remained lower than the overall IR of all hospitalizations.

Discussion

Using data from a population-based database in Hong Kong, we described the burden of cardiovascular outcomes, hospitalization, and costs amongst Asian users of ICI. The IR of MACE was low and cardiovascular hospitalizations and costs contributed to only a small proportion of all hospitalizations and related costs. Importantly, the IR of MACE and cardiovascular hospitalization were both higher during the first year of follow-up, and the most occurrences of MACE were within the first year of follow-up.

Our findings suggested that ICI-related cardiotoxicity is uncommon among Asian users of ICI. Cardiovascular hospitalizations accounted for only 0.5% of all hospitalization episodes, contrasting published governmental figures in 2019, when hospitalizations and deaths from cardiovascular causes accounted for 7.6% of such events.[15] This was in agreement with the general consensus that ICI-related cardiotoxicity is uncommon: a recent meta-analysis of 51 trials found an incidence of 3.1%-5.8% amongst patients using ICI.[16] Meanwhile, another meta-analysis of 63 trials found even lower incidence for MI (0.74 per 100 patients), HF (0.87 per 100 patients), and stroke (0.88 per 100 patients),[17] comparable to the

rates we observed. In addition, previous studies observed that most ICI-related cardiotoxic events occurred shortly after initiation of ICI,[18,19] which was echoed by our finding that 77.6% of MACE occurred within the first year after initiating ICI. These findings should aid clinicians during their discussion of therapeutic options with patients eligible for ICI, allowing clinicians to better inform patients of the risks involved and thereby facilitate shared decision-making. Furthermore, the finding that the majority of MACE among patients treated with ICI occurs within the first year of ICI initiation underscores the importance of close cardiology follow-up as well as clinician- and patient-level education regarding symptoms that would be suggested of MACE. Indeed, these findings highlight the importance of synergy between oncology and cardiology care providers.

The low frequency of ICI-related cardiotoxicity does not undermine its clinical importance. Studies have observed mortality rates between 27% and 53% amongst patients with ICI-related cardiotoxicity, making it one of the deadliest ICI-related side effects.[18-21] This has fueled ample research of ICI-related cardiotoxicity, with some exploring therapeutic options which, given the inflammatory nature of the condition, have mostly revolved around glucocorticoids and immunosuppressants, in addition to cessation of ICI.[19,22-24]

The rarity of ICI-related cardiotoxicity, however, did mean that it is methodologically and statistically difficult to identify its risk factors – knowing the risk factors is crucial for effectively managing ICI users as it allows better stratification of patients at high risk of ICI-related cardiotoxicity, to whom resources may be better allocated for closer monitoring and better optimization of cardiovascular conditions. A case series by Mahmood and colleagues suggested that pre-existing cardiovascular conditions may predispose to ICI-related cardiotoxicity,[25] while a pharmacovigilance study observed that most patients who had ICI-related cardiotoxicity did not have pre-existing cardiovascular conditions.[20] Jain and colleagues attempted to identify risk factors for adverse cardiovascular outcomes in ICI users,[26] with the type of ICI used, specific types of cancer, and other autoimmunity-related conditions such as thyroiditis, instead of pre-existing cardiovascular conditions, being associated with adverse cardiovascular outcomes.[26] These results nonetheless remain to be validated in other cohorts, underscoring the need to evaluate data from diverse and global patient populations. Brumberger and colleagues also attempted to elucidate the risk factors using multivariable logistic regression, and identified female gender, African American race, and smoking as risk factors for ICI-related cardiotoxicity.[21] Nonetheless, they

considered a small number of cardiovascular risk factors, which limited the relevance of the results. Our findings appeared to support the observation by Mahmood and colleagues, with those who had MACE having more cardiovascular risk factors and used more cardiovascular and antidiabetic medications at baseline. Nonetheless, the low event rate precluded any clinically meaningful multivariable regression analysis. Overall, the risk factors for ICI-related cardiotoxicity remain a critical gap in the literature that urgently requires further investigations. In the broader sense, other tools of risk stratification, which may include risk scores or novel biomarkers,[27] warrant further exploration and investigation as well.

To the best of our knowledge, this was one of the first studies to specifically quantify the risk of cardiovascular outcomes and the IR and cost of hospitalization amongst Asian ICI users. With the emerging evidence of racial and ethnic disparity in ICI-related adverse events,[28,29] race / ethnicity-specific quantification of the risk of ICI-related cardiotoxicity and cardiovascular hospitalization is much needed. Although Li and colleagues previously described the incidence of ICI-related adverse events in Chinese patients, cardiovascular events were not reported specifically, and the sample size (1063 patients) limited the generalizability of their findings.[7] Having used data from a large, representative, population-based database in Hong Kong, our cohort essentially included all patients that were treated with ICI in Hong Kong. Our findings thus closely reflected real-world practice and may be more generalizable to other regions in Asia. Further studies from other regions of Asia are required to validate our findings, and comparison against findings from other regions may allow better understanding of the determinants underlying the racial and ethnic disparities in ICI-related cardiotoxicity.

Limitations

This study has several limitations. First, cancer staging was not available, which limited the interpretation and applicability of our findings. Nonetheless, ICI are generally used for advanced disease, and given that this study set out to describe the overall epidemiology of MACE and hospitalizations amongst users of ICI, our findings remain valid and clinically relevant. Second, all diagnoses and outcomes were defined using ICD codes and could not be individually adjudicated. Nonetheless, all data were input by the treating clinicians independent of the authors, and none of the authors had the authority to influence data input. CDARS have also been shown to have good coding accuracy and data completeness.[30]

Conclusion

Amongst Asian users of ICI, MACE was uncommon, and a small proportion of hospitalizations and related costs was attributable to cardiovascular causes. Most of the MACE and cardiovascular hospitalizations occurred during the first year after initiating ICI. Further studies on risk stratification and race / ethnicity-specific investigation of ICI-related cardiotoxicity are warranted.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2022.101380.

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