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Cardiovascular and venous thromboembolism risks in cancer patients treated with immune checkpoint inhibitors compared to non-users- a multi-center retrospective study

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Abstract

Background Immune Checkpoint Inhibitors (ICIs) have revolutionized cancer therapy. This study examines the cardiovascular risks of ICIs compared to non-ICI therapies.

Methods Utilizing the Chang Gung Research Database (CGRD) of Taiwan, this retrospective study analyzed 188,225 cancer patients, with 1,737 undergoing ICI treatment from January 1, 2008, to June 30, 2021. Through 1:1 propensity score matching (PSM), we compared specific outcomes between patients treated with ICIs and those who were not. The analysis also accounted for the competing risk of mortality in assessing the results after PSM. The observation period spanned from this index date to whichever came first: the date of the specific outcomes, the last follow-up recorded, or the end date of the study on June 30, 2022.

Results The study found no significant increase in the risk of cardiac death, non-fatal myocardial infarction, heart failure hospitalization, deep vein thrombosis, or pulmonary embolism in patients treated with ICIs as compared to those receiving non-ICI therapy. Interestingly, ICI treatment was linked to a lower risk of non-fatal stroke (0.27% per year vs. 0.46% per year; subdistribution hazard ratio = 0.59; 95% confidence interval = 0.35–0.98; $P = 0.0430$). Furthermore, subgroup analysis revealed that the ICI group had a decreased risk of cardiac death in patients with cancers other than head and neck cancer, and a reduced risk of stroke among diabetic patients.

Conclusions ICIs do not significantly elevate the risk of cardiovascular events in cancer patients and may lower the stroke risk, underscoring the need for additional prospective studies to clarify these findings.

Keywords Immune checkpoint inhibitor, Cancer, Stroke, Myocardial infarction, Heart failure, Deep vein thrombosis, Pulmonary embolism

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Background

Immune Checkpoint Inhibitors (ICIs) are monoclonal antibody agents that activate and enhance the host immune system for targeting and killing cancer cells, they block different checkpoint proteins including cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed cell death ligand 1 (PD-L1). Despite its success in cancer treatment, ICIs led to nonspecific activation of the immune system involving vital organs, causing several immune-related adverse events [1]. ICIs associated cardiotoxicity can be presented as myocarditis, pericarditis, Takotsubo cardiomyopathy, myocardial infarction, arrhythmias, and conduction disorders [2], which could be explained by cross-reactivity between the tumor antigen and cardiac antigen [3, 4] and immune-mediated responses, including inflammatory cell infiltration and myocardial fibrosis [5]. In addition, these immune checkpoints are critical negative regulators of atherosclerosis, and inhibiting these key pathways in atherosclerosis may lead to an increase in atherosclerotic plaque and atherosclerosis-related cardiovascular events [6].

Several studies have investigated the impact of ICI-related adverse cardiovascular events. In a meta-analysis study, patients prescribed with ICI had an increased risk of heart failure hospitalization (HFH), myocardial infarction (MI), and ischemic stroke compared with non-ICI patients [7]. Cho-Han Chiang et al. reported that ICIs were associated with increased risks of adverse cardiovascular events, particularly ischemic stroke and pulmonary embolism (PE) in Asian populations [8]. However, these data were still limited to make conclusions and should be investigated in detail. Thus, the present study aims to investigate the risks of cardiovascular events in patients treated with ICIs versus non-ICIs.

Methods

Database

This study utilized data from the Chang Gung Research Database (CGRD), which comprises comprehensive patient-level medical records from the Chang Gung Memorial Hospital (CGMH). As the largest healthcare provider in Taiwan, the CGMH network includes four tertiary care centers and three primary teaching hospitals, boasting nearly 10,000 hospital beds and admitting approximately 280,000 patients each year. In 2015, CGMH accounted for around 10% of Taiwan's medical services, with 500,000 visits to the emergency department and 8.6 million outpatient visits [9]. The CGRD offers extensive medical records for each patient, encompassing diagnoses, imaging studies, laboratory tests, medications, and medical procedures. To protect privacy, all personal patient information was anonymized through a uniform encryption process, obviating the need for informed consent for this research. The Chang-Gung Medical Foundation's Institutional Review Board granted approval for this study (CGMH IRB No. 202101057B0), and the requirement for informed consent was accordingly waived.

Study design

We focused on adults aged 18 and older who were diagnosed with cancer, either as a primary or secondary condition, and who underwent any form of cancer treatment. These individuals were identified within the CGRD from January 1, 2008, to June 30, 2021. The study distinguished between patients based on their treatment with ICIs, which include: [1] CTLA-4 inhibitors: ipilimumab; [2] PD-1 inhibitors: pembrolizumab and nivolumab; and [3] PD-L1 inhibitors, including atezolizumab, avelumab, and durvalumab. Those who received ICI therapy were classified into the ICI therapy group, while patients who did not receive ICI treatment were placed in the non-ICI therapy group. From the CGRD's Cancer Registry Database, after excluding individuals younger than 18 years old or those without follow-up data, we initially identified 188,225 cancer patients, of which 1,737 had undergone ICI treatment and 186,488 of non-ICI treated controls from January 1, 2008, to June 30, 2021. Through propensity score matching (PSM), we included 1,714 patients in the ICI treatment group and an equal number in the non-ICI treatment group for comparative analysis, as detailed in Table 1. The commencement of ICI treatment was marked as the index date for the ICI group. For those in the non-ICI group, the index date was aligned to match their ICI counterparts based on the aforementioned characteristics. The observation period spanned from this index date to whichever came first: the date of the specific outcome, the last follow-up recorded in the CGRD, or the end date of the study on June 30, 2022.

Study outcomes

This study aimed to investigate the occurrence of adverse cardiovascular events, which consist of cardiac death, non-fatal stroke, non-fatal MI, and HFH. Additionally, it assessed thromboembolism events, including deep vein thrombosis (DVT) and PE. To guarantee precision and prevent incorrect classifications, the identification of all study outcomes was strictly based on discharge diagnoses. Initially, these codes followed the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) system. After January 1, 2016, the system transitioned to using the Tenth Revision (ICD-10-CM) codes. The specific ICD-9-CM and ICD-10-CM codes utilized to identify both the adverse cardiovascular events under study and the baseline covariates are detailed in Supplemental Table I.

Table 1 Clinical characteristics of patients treated with Immune checkpoint inhibitor therapy Versus Non-immune checkpoint inhibitor therapy before and after propensity score matching (PSM)

	Before PSM							After PSM						
	Total population (*N* = 188,225)		Immune checkpoint inhibitor therapy (*N* = 1,737)		Non- immune checkpoint inhibitor therapy (*N* = 186,488)		ASMD	Total population (*n* = 3,428)		Immune checkpoint inhibitor therapy (*n* = 1,714)		Non- immune checkpoint inhibitor therapy (*n* = 1,714)		ASMD
	n	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Demographics														
Age, years	60.40 ± 13.91		62.61 ± 12.72		60.38 ± 13.92		0.1672	62.49 ± 13.05		62.63 ± 12.7		62.35 ± 13.39		0.0215
Male	99,840	53.04	1,160	66.78	98,680	52.91	0.2858	2278	66.45	1139	66.45	1139	66.45	0.0000
BMI, kg/m^2	24.26 ± 4.13		23.37 ± 3.80		24.27 ± 4.14		0.2265	23.32 ± 3.76		23.38 ± 3.79		23.26 ± 3.72		0.0320
Smoking	18,266	9.70	395	22.74	17,871	9.58	0.3634	770	22.46	376	21.94	394	22.99	0.0252
Cancer types														
Solid tumors														
Lung	17,885	9.50	359	20.67	17,526	9.40	0.3193	695	20.27	350	20.42	345	20.13	0.0072
Hepatobiliary	21,429	11.38	332	19.11	21,097	11.31	0.2185	642	18.73	326	19.02	316	18.44	0.0149
Head and Neck	24,758	13.15	258	14.85	24,500	13.14	0.0493	528	15.40	254	14.82	274	15.99	0.0324
Others*	115,855	61.55	773	44.50	115,082	61.71	0.3501	1522	44.40	769	44.87	753	43.93	0.0189
Hematologic malignancy	8298	4.41	15	0.86	8,283	4.44	0.2243	41	1.20	15	0.88	26	1.52	0.0588
Stage 4 grading	38,850	21.25	592	35.05	38,258	21.12	0.3137	1169	35.11	577	34.63	592	35.58	0.0199
Received surgery	29,941	15.91	446	25.68	29,495	15.82	0.2450	834	24.33	435	25.38	399	23.28	0.0490
Received radiation therapy	10,267	5.45	359	20.67	9,908	5.31	0.4693	680	19.84	340	19.84	340	19.84	0.0000
Received chemotherapy	20,103	10.68	586	33.74	19,517	10.47	0.5842	1128	32.91	563	32.85	565	32.96	0.0023
Comorbidities														
Hypertension	41,128	21.85	641	36.90	40,487	21.71	0.3385	1219	35.56	627	36.58	592	34.54	0.0426
DM	23,870	12.68	378	21.76	23,492	12.60	0.2446	752	21.94	362	21.12	390	22.75	0.0394
Dyslipidemia	19,365	10.29	243	13.99	19,122	10.25	0.1148	449	13.10	235	13.71	214	12.49	0.0362
Previous MI	1,950	1.04	21	1.21	1,929	1.03	0.0171	38	1.11	20	1.17	18	1.05	0.0115
Previous stroke	7,921	4.21	53	3.05	7,868	4.22	0.0625	99	2.89	53	3.09	46	2.68	0.0245
Previous PCI	1,260	0.67	15	0.86	1,245	0.67	0.0218	30	0.88	14	0.82	16	0.93	0.0118
Previous CABG	134	0.07	1	0.06	133	0.07	0.0039	1	0.03	1	0.06	0	0.00	0.0347
Severity of Chronic kidney disease														
Mild (eGFR:45–59)	15,028	8.15	194	11.18	14,834	8.12	0.1038	385	11.29	189	11.03	196	11.55	0.0164
Moderate(eGFR:30–44)	7,189	3.90	99	5.70	7,090	3.88	0.0853	183	5.37	98	5.72	85	5.01	0.0315
Severe (eGFR:15–29)	3,386	1.84	54	3.11	3,332	1.82	0.0833	99	2.90	53	3.09	46	2.71	0.0226
End stage renal disease	4,675	2.54	58	3.34	4,617	2.53	0.0480	111	3.26	58	3.39	53	3.12	0.0152
LVEF, %	70.75 ± 9.01		71.86 ± 8.02		70.73 ± 9.02		0.1324	72.04 ± 7.88		71.91 ± 7.97		72.18 ± 7.78		0.0343
Systolic blood pressure, mmHg	131.61 ± 21.60		128.76 ± 20.95		131.64 ± 21.60		0.1354	128.37 ± 21.3		128.98 ± 20.92		127.72 ± 21.69		0.0591
Diastolic blood pressure, mmHg	75.55 ± 12.49		74.73 ± 12.22		75.56 ± 12.50		0.0671	74.65 ± 12.5		74.81 ± 12.22		74.49 ± 12.78		0.0256
Glycohemoglobin, %	6.51 ± 1.55		6.29 ± 1.23		6.51 ± 1.55		0.1572	6.29 ± 1.24		6.29 ± 1.24		6.29 ± 1.24		0.0000

Table 1 (continued)

	Before PSM							After PSM						
	Total population (*N* = 188,225)		Immune checkpoint inhibitor therapy (*N* = 1,737)		Non- immune checkpoint inhibitor therapy (*N* = 186,488)		ASMD	Total population (*n* = 3,428)		Immune checkpoint inhibitor therapy (*n* = 1,714)		Non- immune checkpoint inhibitor therapy (*n* = 1,714)		ASMD
	n	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	
Cardiovascular Medications														
Aspirin	12,353	6.56	117	6.74	12,236	6.56	0.0072	216	6.30	113	6.59	103	6.01	0.0239
Clopidogrel	4,033	2.14	63	3.63	3,970	2.13	0.0898	130	3.79	62	3.62	68	3.97	0.0183
Ticagrelor	196	0.10	5	0.29	191	0.10	0.0431	7	0.20	3	0.18	4	0.23	0.0111
Statin	13,168	7.00	183	10.54	12,985	6.96	0.1270	356	10.39	179	10.44	177	10.33	0.0036
ACEI or ARB	18,082	9.61	261	15.03	17,821	9.56	0.1672	503	14.67	256	14.94	247	14.41	0.0150
Beta-blocker	10,436	5.54	181	10.42	10,255	5.50	0.1825	336	9.80	174	10.15	162	9.45	0.0235
SGLT2-i	430	0.23	18	1.04	412	0.22	0.1038	37	1.08	15	0.88	22	1.28	0.0387
DOACs	1,135	0.60	36	2.07	1,099	0.59	0.1295	68	1.98	31	1.81	37	2.16	0.0251
Warfarin	1,012	0.54	13	0.75	999	0.54	0.0262	25	0.73	12	0.70	13	0.76	0.0070

*, solid cancers such as breast, colorectal, gynecologic, stomach, esophageal, and other types that individually constituted less than 5% of the total were grouped together under the category "Others"

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor antagonist; ASMD = absolute standardized mean difference; CABG = coronary artery bypass graft; DM = diabetes mellitus; DOAC = direct oral anticoagulant; LVEF = left ventricle ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; SGLT2i = sodium–glucose cotransporter-2 inhibitors;

Covariates

For this study, we selected a range of covariates to ensure a comprehensive analysis. These included demographic factors (age and sex), physiological measures (body mass index), the type of cancer diagnosed, a spectrum of cardiovascular comorbidities, the severity of chronic kidney disease (CKD), blood pressure, cardiac function (as measured by left ventricular ejection fraction), blood sugar control (glycohemoglobin levels), and the use of cardiovascular medications. To define comorbidities accurately, we relied on a patient having at least two outpatient diagnoses or one inpatient diagnosis prior to joining the study cohort. Measurements of body weight, height, and blood pressure were taken from nursing records, whether from outpatient visits or hospital admissions. Additionally, we included data from medication records, echocardiograms, and laboratory tests, all collected within six months leading up to the index date, to provide a detailed health profile of each patient at the study's outset.

Statistical analysis

Continuous variables were reported as mean and standard deviation, and categorical data were presented as numbers and percentages. For confounding adjustment, we employed propensity score matching (PSM) to mitigate the confounding effects between the two groups. To ensure a fair comparison between groups, we assessed the balance of potential confounders at the baseline using the absolute standardized mean difference (ASMD) rather than conventional statistical tests. This choice is predicated on the understanding that balance is a characteristic of the sample itself, not of any hypothetical underlying population. An ASMD value of 0.1 or lower was considered indicative of negligible differences in confounders between the groups [10]. Of note, solid cancers such as breast (1.84%), colorectal (4.43%), gynecologic (4.2%), stomach (3.8%), esophageal (2.3%), pancreatic (1.15%), melanoma (0.9%), and other types that individually constituted less than 5% of the total ICI therapy were grouped together under the category "Others". We compared the risks of then major adverse cardiovascular events and venous thromboembolism between the groups using Cox proportional hazards models. Given the high mortality rate observed among cancer patients in our study (40.25 per 100 person-years in the ICI group and 15.55 in the non-ICI group), we adjusted our analysis for the competing risk of death when evaluating all study outcomes after PSM. The study outcomes were estimated using the subdistribution hazard ratio (sub-HR) calculated through Fine-Gray competing risks regression analysis, with significance assessed using the Gray test [11]. Since the ASMDs of the listed confounding factors were all less than 0.1 after PSM, only univariate competing risk analysis was conducted in Table 2, without adjusting for

Table 2 Clinical outcomes for Cancer patients receiving Immune checkpoint inhibitor therapy compared to those not receiving Immune checkpoint inhibitor therapy after propensity score matching

Clinical outcomes	Immune checkpoint inhibitor therapy	Non- immune checkpoint inhibitor therapy	sub-HR (95% CI)	*p* value
	(*n* = 1714)	(*n* = 1714)		
Adverse cardiovascular events				
Cardiac death	20 (0.24)	31 (0.37)	0.65 (0.37–1.13)	0.1259
Non-fatal myocardial infarction	13 (0.15)	15 (0.18)	0.87 (0.41–1.82)	0.7057
Non-fatal stroke	23 (0.27)	39 (0.46)	0.59 (0.35–0.98)	0.0430
Hospitalization for heart failure	27 (0.32)	30 (0.35)	0.90 (0.54–1.52)	0.6997
Venous thromboembolism				
Deep vein thrombosis	51 (0.61)	55 (0.66)	0.93 (0.64–1.37)	0.7188
Pulmonary embolism	20 (0.24)	13 (0.15)	1.54 (0.77–3.10)	0.2230

Data presented as number (Incidence rate, per 100 person-year)

CI = confidence interval; sub-HR = subdistribution hazard ratio

other factors. A subgroup analysis was also performed to assess whether the sub-HR of study outcomes for the ICI and Non-ICI treatment groups was consistent across the pre-specified subgroups, including gender, diabetes mellitus (DM), CKD, lung cancer, hepatobiliary cancer, head and neck cancer, and hematologic malignancy. A P-value of less than 0.05 was deemed to indicate statistical significance. Data processing and analysis were performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Between January 1, 2008, and June 30, 2022, a total of 188,225 cancer patients were identified for this analysis, of which 1,737 had undergone ICI treatment and 186,488 had not. Before PSM, the three most prevalent cancers among patients treated with ICI were lung (20.67%), hepatobiliary (19.11%), and head and neck (14.85%). Patients in the ICI group were observed to have a higher incidence of undergoing surgery, radiation therapy, and chemotherapy. They also showed a greater prevalence of hypertension, DM, and dyslipidemia, alongside higher prescription rates for statins and ACE inhibitors or angiotensin receptor blockers (ACEI/ARB) compared to the non-ICI group. Moreover, the ICI group exhibited a larger proportion of patients with mild CKD, higher left ventricular ejection fraction values, lower systolic blood pressure, and reduced glycohemoglobin levels than those in the non-ICI group. After PSM, the cohort was narrowed down to 3,428 patients—1,714 treated with ICIs and 1,714 not treated with ICIs—boasting well-balanced baseline characteristics across all variables, as evidenced by ASMD of less than 0.1. Table 1 presents the clinical characteristics of the study population both before and after PSM.

Cardiovascular and venous thromboembolism outcomes

In analyzing adverse cardiovascular events, the ICI group had comparable risks of cardiac death (0.24% per year versus 0.37% per year; sub-HR = 0.65; 95% confidence interval [CI] = 0.37–1.13; *P* = 0.1259), non-fatal MI (0.15% per year versus 0.18% per year; sub-HR = 0.87; 95% CI = 0.41–1.82; *P* = 0.7057), and HFH (0.32% per year versus 0.35% per year; sub-HR = 0.90; 95% CI = 0.54–1.52; *P* = 0.6997) compared with the non-ICI group. However, the ICI group exhibited a significantly lower risk of non-fatal stroke compared to the non-ICI group (0.27% per year vs. 0.46% per year; sub-HR = 0.59; 95% CI = 0.35–0.98; *P* = 0.0430). Regarding venous thromboembolism events, the risks of DVT (0.61% per year vs. 0.66% per year; sub-HR = 0.93; 95% CI = 0.64–1.37; *P* = 0.7188) and PE (0.24% per year vs. 0.15% per year; sub-HR = 1.54; 95% CI = 0.77–3.10; *P* = 0.2230) were also comparable between the ICI and non-ICI groups. (Table 2; Figs. 1 and 2).

Subgroup analysis for high risk groups

The subgroup analysis revealed that patients with cancers other than head and neck cancer who were treated with ICI had a lower risk of cardiac death compared to those with head and neck cancer (p interaction = 0.0107; see Supplemental Figure I). Additionally, patients with DM who received ICI treatment had a reduced risk of non-fatal stroke compared to those without DM (p interaction = 0.0239; see Supplemental Figure III). Overall, the subgroup analysis consistently showed similar results for non-fatal MI, DVT, and PE when comparing ICI versus non-ICI treatments across different patient demographics, including gender, DM, CKD, and various cancer types such as lung cancer, hepatobiliary cancer, head and neck cancer, and hematologic malignancy (refer to Supplemental Figures II, IV, V, and VI).

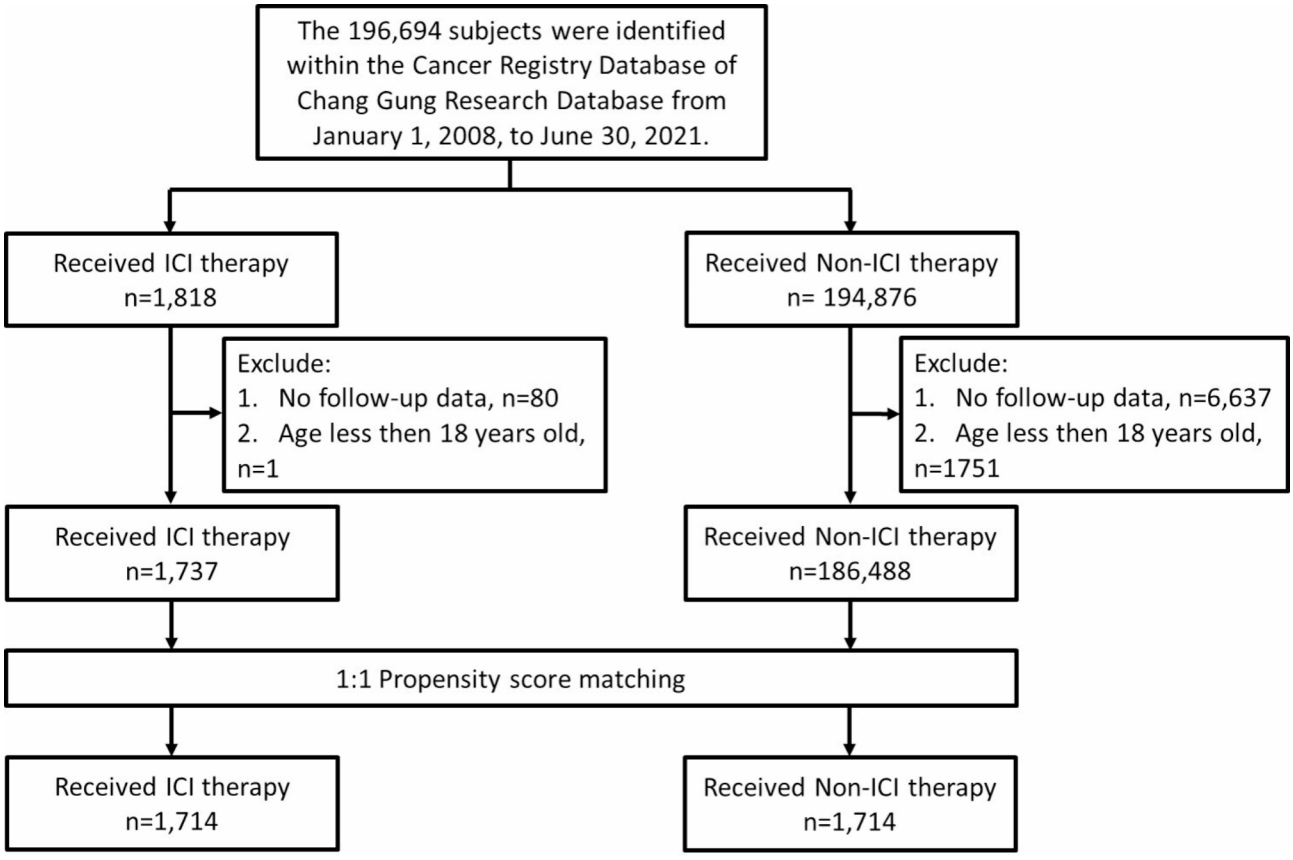

Fig. 1 Enrollment of Cancer Patients Receiving Immune Checkpoint Inhibitor Therapy Compared to Those on Non-Immune Checkpoint Inhibitor Therapy Between January 1, 2008, and June 30, 2022, after excluding individuals younger than 18 years old or those without follow-up data, we initially identified 188,225 cancer patients, of which 1,737 had undergone ICI treatment and 186,488 had not. After propensity score matching (PSM), we included 1,714 patients in the ICI treatment group and an equal number in the non-ICI treatment group for comparative analysis
Abbreviations: ICI = immune checkpoint inhibitor

Discussion

In the large cohort study, the main findings are as follows: First, the use of ICIs had similar risks cardiac death, non-fatal MI, HFH, DVT, and PE compared with non-ICIs group. Second, ICI group showed a significantly lower risk of non-fatal stroke compared to the non-ICI group. Third, by subgroup analysis, patients with cancers other than head and neck cancer who underwent ICI treatment exhibited a significantly lower risk of cardiac death compared to those with head and neck cancer. In addition, our analysis demonstrated a reduced risk of non-fatal stroke among patients with diabetes treated with ICI compared to those without diabetes. These findings underscores the importance of considering tumor site when evaluating the cardiovascular effects of ICI therapy and suggest a potential association between ICI therapy and a reduced risk of stroke, particularly among patients with DM.

Before PSM, that patients treated with ICI therapy had higher rates of medication use, including statins and ACEI/ARB. These medications are known for their cardioprotective effects and may reduce cardiotoxicity in cancer patients [12, 13]. Additionally, the ICI group exhibited higher left ventricular ejection fraction, lower systolic blood pressure, and lower glycohemoglobin levels compared to the non-ICI group, which are considered beneficial for cardiovascular health. To address these potential confounding factors, we conducted PSM. Since the ASMDs of the listed confounding factors were all less than 0.1 after PSM. This approach was implemented to minimize bias and ensure a more accurate comparison of outcomes between the ICI and non-ICI groups.

Several studies have brought to light the potential risks associated with these therapies, particularly concerning adverse cardiovascular events. For instance, Drobni et al. conducted a significant single-center study, analyzing 2,842 patients over a 2-year period. Their findings indicated a marked increase in cardiovascular risks among those treated with ICIs, with a seven-fold and four-fold escalation in the risks of MI and stroke, respectively [6]. Similarly, a retrospective analysis in an Asian cohort by Cho-Han Chiang et al. underscored this concern,

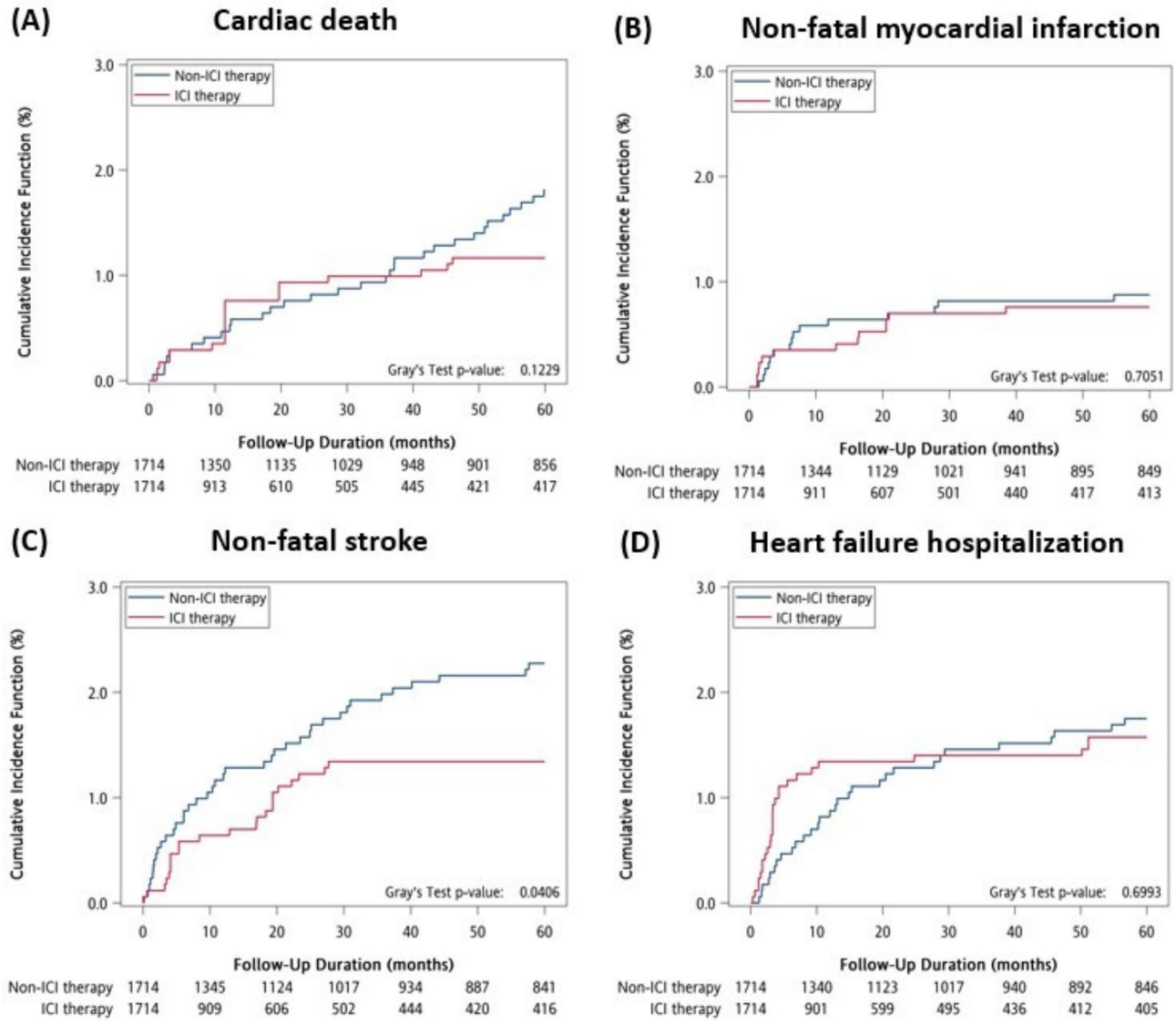

Fig. 2 Cumulative Incidence Curves for Cardiovascular Outcomes in Cancer Patients: Comparing Immune Checkpoint Inhibitor Therapy to Non-Immune Checkpoint Inhibitor Therapy After Propensity Score Matching

Cumulative incidence curves of specific outcomes for cancer patients are depicted in Fig. 2. The outcomes examined include (**A**) Cardiac death, (**B**) Non-fatal MI, (**C**) Non-fatal stroke, and (**D**) HFH. The study show that ICI group exhibited comparable cumulative risks of cardiac death, non-fatal MI, and HFH compared to the non-ICI group. ICI group demonstrated a lower annual event rate of non-fatal stroke in the ICI group compared to the non-ICI group
Abbreviations: HFH = heart failure hospitalization; ICI = immune checkpoint inhibitor; MI = myocardial infarction

demonstrating an augmented risk of cardiovascular events, especially ischemic stroke and PE, in 1,736 cancer patients receiving ICI therapy [8]. Contrasting these findings, the most comprehensive meta-analysis to date, encompassing 21 randomized controlled trials (RCTs) with a combined cohort of 8,633 cases and 6,607 controls, alongside three observational studies with 13,686 cases and 23,183 controls, painted a more nuanced picture. While RCTs suggested a marginal association between ICI use and an increased odds of MI, observational studies did not corroborate this risk. Furthermore, neither study design found a significant association between ICI therapy and stroke risk [14]. Another meta-analysis, specifically investigating neurologic adverse events associated with ICIs, revealed that the overall risk of such events is lower in patients treated with ICIs compared to those undergoing chemotherapy. Additionally, the incidence of stroke events was found to be low (<1%) in both the ICI and non-ICI groups, aligning with the findings of our study [15]. Our investigation diverges from these earlier findings, presenting a comparative analysis of cardiovascular risks between patients treated with ICIs and those who are not. Interestingly, our study revealed that the ICI group had comparable risks of cardiac death,

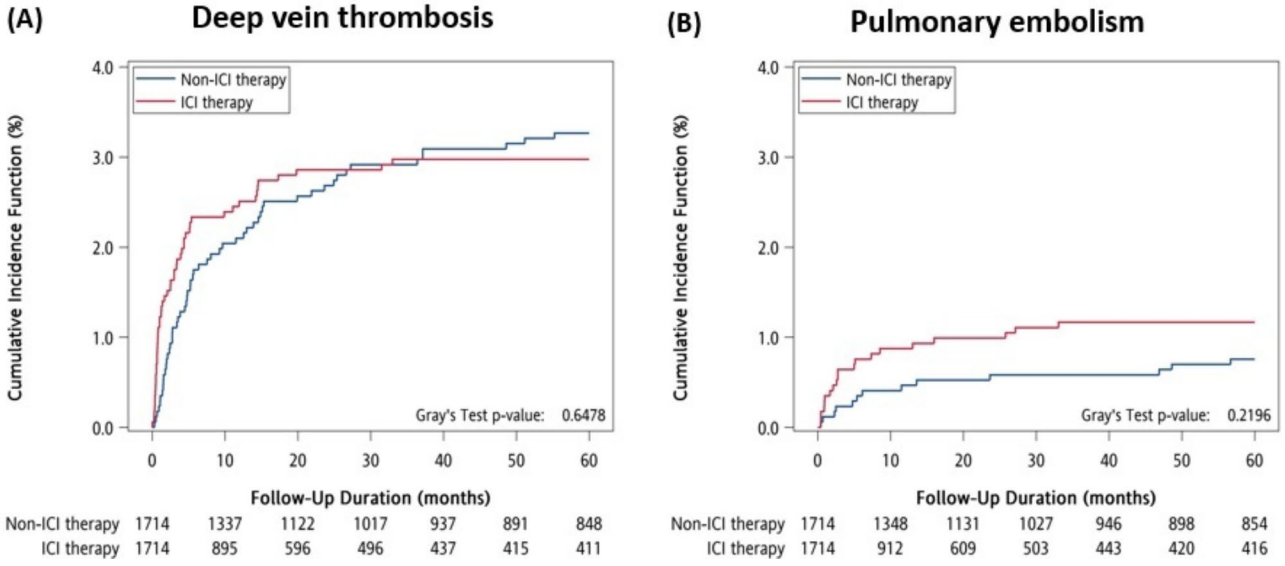

Fig. 3 Cumulative Incidence Curves for Deep Vein Thrombosis and Pulmonary Embolism in Cancer Patients: Comparing Immune Checkpoint Inhibitor Therapy to Non-Immune Checkpoint Inhibitor Therapy After Propensity Score Matching

Cumulative incidence curves of specific outcomes for cancer patients are depicted in Fig. 3. The outcomes examined include (**A**) DVT and (**B**) PE. The study show that ICI group exhibited comparable cumulative risks of DVT and PE compared to the non-ICI group

Abbreviations: DVT = deep vein thrombosis; ICI = immune checkpoint inhibitor; PE = pulmonary embolism

MI, HFH, DVT, and PE, albeit with a notably lower risk of stroke. This disparity in findings could be attributed to the methodological considerations of our study, including the analysis of cardiovascular outcomes amidst the competing risk of death prevalent in the cancer population. Such an approach provides a critical perspective on the cardiovascular safety profile of ICIs, potentially explaining the variance from previous research outcomes. This discrepancy underscores the importance of context in evaluating the safety of ICIs, as well as the need for further research to clarify these associations, especially in populations with high mortality risks such as those afflicted with cancer.

We analyzed the distribution of ICI treatment subtypes among the ICI-treated patients, with the following results: CTLA-4 inhibitors: 38 patients (2.22%), PD-1 inhibitors: 1337 patients (78.00%), PD-L1 inhibitors: 302 patients (17.62%), and combined therapy (CTLA-4, PD-1, or PD-L1 inhibitors): 37 patients (2.16%). To specifically assess whether the lower risk of ischemic stroke is dependent on the type of ICI treatment, we excluded the 37 patients who received combined therapies and analyzed the remaining 3391 patients. In the CTLA-4 inhibitors group, no events of non-fatal stroke were observed. The PD-1 inhibitors group had 16 events (1.20%), with an incidence rate of 0.24 per 100 person-years and a sub-HR of 0.52 (95% CI: 0.29–0.94, $p=0.0290$). The PD-L1 inhibitors group had 5 events (1.66%), with an incidence rate of 0.34 per 100 person-years and a sub-HR of 0.73 (95% CI: 0.29–1.86, $p=0.5070$). The non-ICI therapy group had 39 events (2.28%), with an incidence rate of 0.46 per 100 person-years, serving as the reference group. Notably, patients treated with PD-1 inhibitors showed a statistically significant lower risk of non-fatal stroke compared to those in the non-ICI group, while PD-L1 inhibitors did not demonstrate a statistically significant difference. These results suggest that the observed lower risk of ischemic stroke in the ICI-treated group may indeed vary depending on the specific type of ICI treatment.

Previous studies have suggested that thoracic radiation therapy may increase the risk of MI due to radiation-induced heart disease [16]. In our study, among the 680 patients who received radiation therapy after PSM, 548 (80.59%) received thoracic radiation therapy, while 132 (19.41%) did not. The incidence of non-fatal MI was 0.44% in the overall cohort, with 0.55% in the thoracic radiation group and 0% in the non-thoracic radiation group. The p-value for this comparison was 1.0000, indicating no significant difference in MI risk between the groups. Additionally, previous research has shown that cardiovascular risk in patients with non-metastatic cancer varies by cancer stage [17]. We have analyzed the data with cancer stage as a factor. The results were consistent with our previous analyses, showing no significant difference in outcomes based on cancer stage (data not shown). This suggests that while cancer stage is an important consideration, it does not substantially affect the comparative outcomes between ICI and non-ICI therapies in our study. The higher mortality rate in the ICI group may be influenced by the higher proportion of patients with stage 4 cancer, which is associated with more advanced disease and potentially higher mortality. To address this,

we have employed competing risk analysis to account for the impact of mortality on the follow-up time for cardiotoxic events. Additionally, the median follow-up time differs between the groups, with 0.93 years for the ICI group compared to 3.43 years for the non-ICI group. This shorter follow-up period for the ICI group could contribute to an underestimation of cardiotoxic events.

Our study boasts several notable strengths that enhance the validity and relevance of its findings in the realm of cardiovascular outcomes associated with ICIs. First, the large cohort size and the extensive follow-up period offer a robust dataset for analysis, enabling a comprehensive evaluation of long-term cardiovascular risks. Such scale and scope are crucial for detecting relatively rare events like cardiac death and non-fatal stroke among cancer patients undergoing ICI therapy, thereby providing a solid statistical power to our conclusions. Second, the utilization of the CGRD, with its detailed patient-level medical records, facilitates a nuanced analysis of clinical outcomes. This comprehensive dataset includes diagnoses, imaging studies, laboratory tests, medications, and medical procedures, allowing for an in-depth assessment of cardiovascular events and the potential impact of ICIs. Finally, our investigation into the competing risks of death represents an analytical approach that acknowledges the complex realities of cancer patient outcomes. By adjusting for this factor, we offer a more accurate portrayal of cardiovascular risks, accounting for the high mortality rates inherent to this patient population.

This study has some limitations. First, the use of the CGRD confines our observations to a Taiwanese population treated at Chang Gung Memorial Hospital (CGMH) facilities. While CGMH is a significant healthcare provider in Taiwan, the findings may not be fully generalizable to other populations, especially considering geographical and ethnic differences in cancer prevalence, treatment approaches, and healthcare systems. The specific cancer types and treatment protocols prevalent in Taiwan may differ from those in other countries. Second, as a retrospective database study, our research is inherently limited by the accuracy and completeness of the recorded data. Despite the comprehensive nature of the CGRD, potential inaccuracies in diagnostic coding, missing information, or unrecorded confounders could influence the outcomes. The use of ICD codes may also introduce misclassification bias and reduce the accuracy of event detection, potentially impacting the findings. Although PSM was employed to minimize baseline differences between groups, there remains a possibility of residual confounding due to unmeasured or inadequately captured variables. Third, the high mortality rate among the cancer patient population, particularly those undergoing ICI treatment, introduces competing risks that complicate the analysis of cardiovascular outcomes. Although we adjusted for the competing risk of death in our analysis, this adjustment cannot fully account for the complex interplay between cancer progression, treatment effects, and cardiovascular risk. Fourth, cancer therapies have evolved significantly during the study period from January 1, 2008, to June 30, 2021, potentially influencing patient outcomes. However, detailed data on concomitant cancer therapies were not uniformly available for all patients, and the diversity of cancers treated in our study makes it difficult to clearly distinguish between the different types of chemotherapy. This limitation poses a challenge for comprehensive analysis. Future studies with more detailed treatment data could better elucidate the impact of evolving cancer therapies on these outcomes. Fifth, our study does not differentiate between therapy-naïve patients and those who may have received ICI treatment prior to inclusion in the CGRD. This lack of data could influence the interpretation of treatment outcomes and may introduce variability in the patient cohort. Additionally, information on the duration of ICI therapy was not uniformly available for all patients. The duration of treatment could significantly affect patient outcomes, as longer exposure may lead to different cardiovascular risks compared to shorter treatment periods.

Conclusions

In conclusion, our study demonstrates that ICIs did not significantly increase the risk of major cardiovascular events in cancer patients, compared with non-ICI therapies in a large cohort of cancer patients. Furthermore, our findings suggest that ICIs might reduce the risk of non-fatal stroke. To confirm these observations, further prospective or randomized studies are warranted.

Supplementary Information

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Supplementary Material 1

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Author contributions

JRP, CC, HFL, and CHH contributed to the conception and design of the study, as to well as the analysis and interpretation of the data. They wrote the manuscript and approved its submission. CHH, CHC, and YCW contributed to the acquisition and analysis. CHH and HFL contributed to the data analysis and provided critical revisions. CC, CHH, CHC, HCS, and TYC contributed to the conception and design of the study and provided critical revisions of the article for important intellectual content. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Our research was conducted in accordance with the Declaration of Helsinki. The Chang-Gung Medical Foundation's Institutional Review Board granted approval for this study (CGMH IRB No. 202101057B0), and the requirement for informed consent was accordingly waived.

Consent for publication
To protect privacy, all personal patient information was anonymized through a uniform encryption process, obviating the need for informed consent for this research.

Competing interests
The authors declare no competing interests.

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