Adverse Cardiovascular Complications Following Prescription of Programmed Cell Death 1 (PD-1) and Programmed Cell Death Ligand 1 (PD-L1) Inhibitors: A Propensity-Score Matched Cohort Study With Competing Risk Analysis

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Abstract

Background: Programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors, such as pembrolizumab, nivolumab and atezolizumab, are major classes of immune checkpoint inhibitors that are increasingly used for cancer treatment. However, their use is associated with adverse cardiovascular events. We examined the incidence of new-onset cardiac complications in patients receiving PD-1 or PD-L1 inhibitors.

Methods: Patients receiving PD-1 or PD-L1 inhibitors since their launch up to 31st December 2019 at the Hospital Authority of Hong Kong, without pre-existing cardiac complications were included. The primary outcome was a composite of incident heart failure, acute myocardial infarction, atrial fibrillation or atrial flutter with the last follow-up date of 31st December 2020. Propensity score matching between PD-L1 inhibitor use and PD-1 inhibitor use with a 1:2 ratio for patient demographics, past comorbidities and non-PD-1/PD-L1 medications was performed.

Results: A total of 1959 patients were included. Over a median follow-up of 247 days (interquartile range [IQR]: 72-506), 320 (incidence rate [IR]: 16.31%) patients met the primary outcome after PD-1/PD-L1 treatment: 244 (IR: 12.57%) with heart failure, 38 (IR: 1.93%) with acute myocardial infarction, 54 (IR: 2.75%) with atrial fibrillation, 6 (IR: 0.31%) with atrial flutter. Compared with PD-1 inhibitor treatment, PD-L1 inhibitor treatment was significantly associated with a lower risk of composite outcome both before (hazard ratio [HR]: 0.32, 95% CI: [0.18-0.59], P value=0.0002) and after matching (HR: 0.34, 95% CI: [0.18-0.65], P value=0.001), and lower all-cause mortality risk before matching (HR: 0.77, 95% CI: [0.64-0.93], P value=0.0078) and after matching (HR: 0.80, 95% CI: [0.65-1.00], P value=0.0463). Patients who developed cardiac complications had shorter average readmission intervals and a higher number of hospitalizations after treatment with PD-1/PD-L1 inhibitors both before and after matching (P value<0.0001). Competing risk analysis with cause-specific hazard and subdistribution hazard models, and multiple approaches based on the propensity score all confirmed these observations.

Conclusions: Compared with PD-1 treatment, PD-L1 treatment was significantly associated with lower risk of new onset cardiac composite outcome and all-cause mortality both before and after propensity score matching.

Introduction

The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway is one of the major immune checkpoints for mitigating the immune response to prevent autoimmunity. However, cancer cells often devise strategies to hijack these mechanisms to evade anti-tumor immunity. In this regard, inhibitors of PD-1 (e.g., pembrolizumab, nivolumab, cemiplimab) and PD-L1 (e.g. atezolizumab, avelumab, durvalumab) have shown clinical efficacies against different types of solid tumors, including melanoma, non-small cell lung cancer (NSCLC), urothelial carcinoma and bladder cancer. Pembrolizumab is also the first agent to receive a “pan-cancer” approval by the United States Food and Drug Administration (FDA) for the treatment of unresectable or metastatic solid tumors that have high microsatellite instability or mismatch repair deficiency.

Despite their treatment efficacy in clinical oncology, immune-related adverse events associated with the use of immune checkpoint inhibitors (ICIs) are now increasingly recognized (1–4). Adverse events include atherosclerosis, colitis, hepatitis, adrenocorticotrophic hormone insufficiency, hypothyroidism, type 1 diabetes mellitus, and acute kidney injury (5–7). To this end, cardiovascular complications are estimated to constitute approximately 2% of ICI-related adverse drug reactions (8). The commonest is myocarditis, but other cardiovascular abnormalities reported are left ventricular dysfunction, acute myocardial infarction (AMI), cardiac arrhythmias and heart failure (9). These cardiovascular complications typically present with clinical heterogeneity, and in turn account for the high morbidity and mortality rates observed in such patient cohorts. Whilst cardiotoxicity is being documented with an increasing frequency, their cumulative incidence rates remain largely unexplored. In this territory-wide study, we examined the incidence of cardiovascular events of incident heart failure, acute myocardial infarction, atrial fibrillation or atrial flutter in cancer patients receiving PD-1 or PD-L1 inhibitors.

Methods

Study Population

This study was approved by The Joint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee. Patients receiving PD-1 or PD-L1 inhibitors since their launch up to 31st December 2020 at the Hospital Authority of Hong Kong, without pre-existing cardiac complications were included. Patient data were obtained using the electronic health record database, which is connected to the territory-wide Clinical Data Analysis and Reporting System (CDARS). The system is an integrative centralized platform that permits the extraction of clinical data for analysis and reporting. The system attributes each patient a unique reference identification number, allowing for the retrieval of comprehensive medical records, including disease diagnoses, clinical comorbidities, laboratory parameters and operative procedures. Patients or the public were not involved in any aspect of this study. The system has been previously used by both our team and other teams in Hong Kong (10–12).

Patient Data

The following clinical data were extracted: patient characteristics, including demographic details (baseline age and gender), specific pre-existing comorbidities before drug prescriptions, laboratory examinations (including complete blood counts, biochemical tests, lipid and glycemic profiles) were extracted. Past comorbidities from January 1st, 2013 to December 31st, 2020 were extracted, and categorized into hypertension, liver diseases, hip fractures/accident falls, renal diseases, diabetes mellitus, malignant dysrhythmia, chronic obstructive pulmonary disease, ischemic heart disease, peripheral vascular disease, endocrine diseases, gastrointestinal diseases, and stroke/transient ischemic attack. The International Classification of Disease, Ninth Edition (ICD-9) codes that were used to extract the specific comorbidities and outcomes are included in **Supplementary Table 2**. The overall dosage and accumulative duration for patients with new-onset cardiac complications are reported.

Primary outcomes on follow-up

The primary outcome was a composite of incident heart failure, acute myocardial infarction, atrial fibrillation, and atrial flutter. The follow-up period was defined as the first PD-1/PD-L1 prescription date until the primary endpoint or death occurred, or until the end date of August 31st, 2020, whichever was earlier.

Statistical analysis

Continuous variables were presented as median (95% confidence interval [CI] or interquartile range [IQR]) and categorical variables were presented as count (%). The Mann-Whitney U test was used to compare continuous variables. The χ^2 test with Yates' correction was used for 2x2 contingency data, and Pearson's χ^2 test was used for contingency data for variables with more than two categories. The patients with PD-L1 were matched with PD1 controls through propensity score matching of 1:2 ratio, based on patient demographics, Charlson standard comorbidity index, past comorbidities, and non-PD-1/PD-L1 medications. Negligible post-weighting intergroup standardized mean difference (SMD) was defined as SMD < 0.2. To identify the important predictors associated with new-onset cardiac complications of patients after PD-1/PD-L1 treatment, univariate Cox regression was used to calculate hazard ratios (HRs) and 95% CIs. In addition to propensity score matching, the following approaches based on the propensity scores were employed: propensity score stratification (13), inverse probability weighting (14), and high-dimensional propensity score adjustment (15). Paired hospitalization characteristics of patients before and after treatment were compared both in the unmatched and matched cohorts. A two-sided α of < 0.05 was considered statistically significant. Statistical analyses were performed using RStudio software (Version: 1.1.456) and Python (Version: 3.6).

Results

Baseline characteristics

Initially, 2426 cancer patients receiving PD-1/PD-L1 inhibitors were identified (Fig. 1). In total 1959 patients remained in the study cohort after excluding 433 patients with prior cardiac complications and 34 patients who received both PD1 and PDL1 treatments. Propensity score matching with 1:2 ratio between PD-1 and PD-L1 inhibitor use based on demographics, Charlson standard comorbidity index, prior comorbidities, and non-PD-1/PD-L1 medications was performed. This yielded a matched cohort of 663 patients (Table 1).

Table 1. Clinical characteristics of patients with PD-1 use and PD-L1 use before and after 1:2 propensity score matching.

* for SMD 0.2

APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors

	Before matching				After 1:2 matching	
Characteristics	All (N=1959)	PD-L1 users (N=221)	PD-1 users (N=1738)	SMD	All (N=663)	P-value
	Mean(SD);N or Count(%)	Mean(SD);N or Count(%)	Mean(SD);N or Count(%)		Mean(SD);N or Count(%)	
Adverse events						
All-cause mortality	1319(67.33%)	115(52.03%)	1204(69.27%)	0.36*	425(64.10%)	1
Composite outcome	320(16.33%)	11(4.97%)	309(17.77%)	0.41*	91(13.72%)	1
Heart failure	244(12.45%)	10(4.52%)	234(13.46%)	0.32*	75(11.31%)	1
Acute myocardial infarction	38(1.93%)	0(0.00%)	38(2.18%)	0.21*	8(1.20%)	0
Atrial fibrillation	54(2.75%)	1(0.45%)	53(3.04%)	0.2	8(1.20%)	1
Atrial flutter	6(0.30%)	0(0.00%)	6(0.34%)	0.08	2(0.30%)	0
Demographics						
Male gender	1341(68.45%)	165(74.66%)	1176(67.66%)	0.15	498(75.11%)	1
Female gender	618(31.54%)	56(25.33%)	562(32.33%)	0.15	165(24.88%)	5
Baseline age, years	61.0(13.7);n=1959	63.1(10.2);n=221	60.7(14.1);n=1738	0.19	63.0(10.2);n=663	6
<40	151(7.70%)	7(3.16%)	144(8.28%)	0.22*	20(3.01%)	7
[40, 50)	194(9.90%)	13(5.88%)	181(10.41%)	0.17	43(6.48%)	1
[50-60)	481(24.55%)	51(23.07%)	430(24.74%)	0.04	155(23.37%)	5
[60-70)	631(32.21%)	96(43.43%)	535(30.78%)	0.26*	288(43.43%)	9
[70-80)	391(19.95%)	48(21.71%)	343(19.73%)	0.05	133(20.06%)	4
>=80	111(5.66%)	6(2.71%)	105(6.04%)	0.16	24(3.61%)	6
Past comorbidities						
Charlson standard comorbidity index	6.1(3.3);n=1959	6.5(3.1);n=221	6.0(3.3);n=1738	0.16	6.5(3.1);n=663	6
Hypertension	256(13.06%)	29(13.12%)	227(13.06%)	0	88(13.27%)	2
Liver diseases	193(9.85%)	8(3.61%)	185(10.64%)	0.28*	24(3.61%)	8
Hip fractures/accident falls	77(3.93%)	13(5.88%)	64(3.68%)	0.1	37(5.58%)	1
Renal diseases	292(14.90%)	29(13.12%)	263(15.13%)	0.06	85(12.82%)	2
Diabetes mellitus	156(7.96%)	20(9.04%)	136(7.82%)	0.04	60(9.04%)	2
Maligt dysrhythmia	12(0.61%)	0(0.00%)	12(0.69%)	0.12	2(0.30%)	0
Chronic obstructive pulmonary disease	15(0.76%)	2(0.90%)	13(0.74%)	0.02	6(0.90%)	2
Ischemic heart disease	61(3.11%)	5(2.26%)	56(3.22%)	0.06	15(2.26%)	5
Peripheral vascular disease	11(0.56%)	1(0.45%)	10(0.57%)	0.02	3(0.45%)	1
Endocrine diseases	548(27.97%)	56(25.33%)	492(28.30%)	0.07	166(25.03%)	5
Gastrointestinal diseases	1412(72.07%)	184(83.25%)	1228(70.65%)	0.30*	551(83.10%)	1
Stroke/transient ischemic attack	80(4.08%)	8(3.61%)	72(4.14%)	0.03	24(3.61%)	8
Hospitalization						
Average	68.5(194.8);n=1876	53.3(112.0);n=215	70.5(203.0);n=1661	0.1	65.3(202.3);n=647	5

readmission						
Total episode number	14.2(13.9);n=1876	12.2(8.9);n=215	14.5(14.4);n=1661	0.19	13.8(10.9);n=647	1
Overall hospital stay, days	35.2(38.2);n=1876	25.5(22.4);n=215	36.5(39.6);n=1661	0.34*	32.9(31.3);n=647	2
Medications						
PD-L1 v.s. PD-1	221(11.28%)	221(100.00%)	0(0.00%)	inf*	221(33.33%)	2
PD-L1 expenditure, HKD	98251.0(98697.8);n=221	98251.0(98697.8);n=221	-	-	98251.0(98697.8);n=221	9
Total PD-L1 dose amount, mg	12644.1(27488.6);n=221	12644.1(27488.6);n=221	-	-	12644.1(27488.6);n=221	1
PD-L1 inhibitors duration, days	176.0(200.9);n=221	176.0(200.9);n=221	-	-	176.0(200.9);n=221	1
PD-1 expenditure	193878.8(291968.7);n=1750	333403.4(284147.8);n=12	192915.5(291869.7);n=1738	0.49*	203782.5(259059.2);n=454	3
Total PD-1 dose amount (MG)	2817.9(10492.2);n=1750	1450.0(1049.5);n=12	2827.3(10527.4);n=1738	0.18	2454.7(5152.0);n=454	1
PD-1 inhibitors duration, days	202.7(237.7);n=1750	383.3(270.7);n=12	201.5(237.0);n=1738	0.71*	207.7(234.7);n=454	3
Anticoagulants	1108(56.55%)	120(54.29%)	988(56.84%)	0.05	362(54.60%)	1
Steroids	1108(56.55%)	120(54.29%)	988(56.84%)	0.05	362(54.60%)	1
Inflammatory subclinical biomarkers						
Neutrophil-to-lymphocyte ratio	4.6(6.4);n=1952	4.5(9.5);n=221	4.6(5.9);n=1731	0.01	4.3(6.5);n=663	4
Platelet-to-lymphocyte ratio	212.3(243.9);n=1953	203.9(188.4);n=221	213.4(250.1);n=1732	0.04	210.2(304.3);n=663	2
Aspartate transaminase-to-alanine transaminase ratio	1.8(3.6);n=1308	1.1(0.5);n=128	1.9(3.8);n=1180	0.29*	1.5(2.1);n=405	1
Triglyceride glucose index	7.1(0.6);n=580	7.07(0.65);n=67	7.06(0.62);n=513	0.02	7.0(0.6);n=207	7
Urea-to-creatinine ratio	73.1(40.8);n=1937	68.3(23.3);n=221	73.8(42.4);n=1716	0.16	69.5(29.2);n=659	6
Monocyte-to-lymphocyte ratio	0.4(0.5);n=1950	0.4(0.5);n=221	0.5(0.5);n=1729	0.03	0.4(0.4);n=662	0
Complete blood counts						
Mean corpuscular volume, fL	88.0(8.2);n=1953	88.4(7.7);n=221	88.0(8.2);n=1732	0.06	88.2(7.7);n=663	8
Eosinophil, x10 ⁹ /L	0.2(0.3);n=1952	0.2(0.32);n=221	0.18(0.31);n=1731	0.04	0.2(0.3);n=663	0
Lymphocyte, x10 ⁹ /L	1.5(0.9);n=1953	1.6(0.8);n=221	1.5(0.9);n=1732	0.19	1.5(0.7);n=663	1
Metamyelocyte, x10 ⁹ /L	0.8(5.0);n=225	0.5(0.7);n=13	0.8(5.2);n=212	0.07	0.3(0.5);n=72	0
Monocyte, x10 ⁹ /L	0.5(0.3);n=1953	0.54(0.25);n=221	0.53(0.32);n=1732	0.02	0.5(0.3);n=663	0
Neutrophil, x10 ⁹ /L	5.1(3.3);n=1953	5.2(3.4);n=221	5.0(3.3);n=1732	0.05	5.0(3.2);n=663	5
White blood count, x10 ⁹ /L	7.4(5.5);n=1953	7.43(3.3);n=221	7.39(5.74);n=1732	0.01	7.3(3.6);n=663	7
Mean cell haemoglobin, pg	30.7(3.3);n=1953	30.72(3.29);n=221	30.65(3.34);n=1732	0.02	30.8(3.2);n=663	3
Myelocyte, x10 ⁹ /L	0.8(3.1);n=328	1.0(2.0);n=26	0.7(3.2);n=302	0.08	0.6(1.5);n=97	1
Platelet, x10 ⁹ /L	247.9(108.5);n=1953	261.5(92.6);n=221	246.2(110.3);n=1732	0.15	252.6(98.9);n=663	2

Red blood count, x10 ¹² /L	4.4(0.7);n=1953	4.6(0.6);n=221	4.4(0.7);n=1732	0.27*	4.5(0.7);n=663	4
Hematocrit, L/L	0.4(0.1);n=1895	0.4(0.05);n=208	0.38(0.06);n=1687	0.37*	0.4(0.1);n=626	0
<i>Renal and liver functions</i>						
K/Potassium, mmol/L	4.1(0.4);n=1941	4.14(0.43);n=221	4.12(0.44);n=1720	0.04	4.1(0.4);n=661	4
Urate, mmol/L	0.3(0.1);n=627	0.33(0.1);n=43	0.33(0.14);n=584	0.03	0.3(0.1);n=186	0
Albumin, g/L	39.2(5.9);n=1939	39.8(5.4);n=220	39.1(6.0);n=1719	0.11	39.5(5.4);n=660	3
Na/Sodium, mmol/L	139.1(3.8);n=1941	139.4(3.1);n=221	139.1(3.9);n=1720	0.09	139.2(3.4);n=661	1
Urea, mmol/L	5.5(2.4);n=1937	5.3(1.8);n=221	5.6(2.5);n=1716	0.11	5.3(1.8);n=659	5
Protein, g/L	72.1(12.8);n=1853	71.3(16.3);n=207	72.2(12.3);n=1646	0.06	71.7(14.4);n=624	7
Bilirubin, umol/L	13.0(25.3);n=1941	9.5(6.1);n=221	13.4(26.7);n=1720	0.2	11.3(19.1);n=661	9
Creatinine, umol/L	84.9(62.4);n=1952	83.0(37.0);n=221	85.1(64.9);n=1731	0.04	84.8(64.0);n=662	8
SD of creatinine	35.5(103.7);n=1942	29.8(93.9);n=220	36.2(104.9);n=1722	0.06	29.7(82.3);n=658	2
Aspartate transaminase, U/L	54.4(104.9);n=1371	28.3(21.8);n=142	57.5(110.1);n=1229	0.37*	41.2(67.2);n=443	2
SD of aspartate transaminase	59.6(189.6);n=1250	28.6(101.7);n=122	62.9(196.5);n=1128	0.22*	36.5(84.3);n=409	2
Alkaline phosphatase, U/L	108.6(111.6);n=1941	85.2(36.4);n=221	111.6(117.5);n=1720	0.3*	102.1(99.9);n=661	8
SD of alkaline phosphatase	64.8(95.1);n=1928	39.6(75.3);n=220	68.0(96.9);n=1708	0.33*	58.3(89.9);n=655	3
Alanine transaminase, U/L	36.6(55.7);n=1876	28.2(25.1);n=207	37.6(58.3);n=1669	0.21*	31.4(29.5);n=623	2
SD of alanine transaminase	36.4(84.7);n=1855	22.9(50.7);n=201	38.0(87.8);n=1654	0.21*	28.2(51.6);n=612	2
<i>Lipid, iron and calcium profile</i>						
Total iron-binding capacity, L	41.0(12.3);n=103	39.1(11.1);n=5	41.1(12.4);n=98	0.16	42.1(12.7);n=22	3
VitaminB12, pmol/L	453.2(327.2);n=49	447.7(265.6);n=3	453.6(333.2);n=46	0.02	401.2(305.7);n=17	4
Folate, ng/mL	21.7(10.2);n=69	16.0(3.7);n=3	22.0(10.3);n=66	0.78*	20.4(10.4);n=19	1
Ferritin, pmol/L	2546.7(4740.6);n=86	728.2(816.5);n=8	2733.2(4936.4);n=78	0.57*	1941.1(2987.1);n=22	7
Calcium, mmol/L	2.3(0.2);n=1081	2.32(0.13);n=82	2.32(0.16);n=999	0.04	2.3(0.1);n=340	2
SD of calcium	0.1(0.1);n=987	0.07(0.04);n=73	0.1(0.06);n=914	0.49*	0.1(0.1);n=314	0
Phosphate, mmol/L	1.1(0.2);n=948	1.08(0.18);n=61	1.06(0.22);n=887	0.11	1.1(0.2);n=286	1
SD of phosphate	0.2(0.1);n=785	0.1(0.1);n=44	0.2(0.1);n=741	0.41*	0.2(0.1);n=241	0
Inorganic, mmol/L	6.4(8.7);n=259	4.1(5.4);n=24	6.6(8.9);n=235	0.34*	6.5(10.2);n=79	4
SD of inorganic	2.1(3.5);n=113	0.5(0.7);n=13	2.3(3.7);n=100	0.7*	0.8(1.4);n=41	0
<i>Glycemic and clotting profile</i>						
Triglyceride, mmol/L	1.4(1.1);n=598	1.5(1.0);n=68	1.4(1.1);n=530	0.08	1.5(1.2);n=214	1
SD of triglyceride	0.4(0.5);n=294	0.4(0.43);n=30	0.35(0.54);n=264	0.1	0.4(0.6);n=90	0
Glucose, mmol/L	6.3(2.3);n=1773	6.4(2.7);n=206	6.2(2.2);n=1567	0.09	6.3(2.2);n=608	6
SD of glucose	1.5(1.3);n=1638	1.4(1.3);n=194	1.5(1.3);n=1444	0.09	1.5(1.4);n=564	1
HbA1c, g/dL	12.8(2.0);n=1953	13.3(1.7);n=221	12.8(2.0);n=1732	0.31*	13.1(1.9);n=663	1
SD of HbA1c	1.3(0.5);n=1947	1.31(0.54);n=220	1.29(0.54);n=1727	0.05	1.3(0.5);n=660	1

High sensitive troponin-I, ng/L	363.3(10967.7);n=1141	12.7(31.8);n=122	405.3(11605.6);n=1019	0.05	35.5(314.8);n=372	1
SD of high sensitive troponin-I	124.0(1328.2);n=755	18.2(42.4);n=82	136.9(1406.3);n=673	0.12	34.7(207.0);n=245	1
APTT, second	30.8(5.5);n=694	29.1(3.5);n=46	30.9(5.6);n=648	0.39*	30.4(3.9);n=217	2
SD of APTT	2.6(3.1);n=510	1.9(2.3);n=26	2.6(3.2);n=484	0.28*	2.1(1.8);n=152	1
Lactate dehydrogenase, U/L	324.1(422.0);n=1431	315.6(534.6);n=145	325.1(407.6);n=1286	0.02	302.1(354.0);n=466	3
SD of lactate dehydrogenase	155.2(397.1);n=1140	115.6(203.9);n=102	159.1(411.1);n=1038	0.13	121.3(206.3);n=365	1
Total cholesterol, mmol/L	4.6(1.1);n=599	4.9(1.0);n=68	4.5(1.1);n=531	0.29*	4.6(1.1);n=214	4
SD of total cholesterol	0.5(0.4);n=295	0.54(0.43);n=31	0.48(0.44);n=264	0.14	0.5(0.5);n=93	0
Low-density lipoprotein, mmol/L	2.6(0.9);n=583	2.9(0.9);n=65	2.6(0.9);n=518	0.34*	2.7(1.0);n=208	2
SD of low-density lipoprotein	0.4(0.4);n=283	0.5(0.4);n=29	0.4(0.4);n=254	0.18	0.4(0.4);n=88	0
High-density lipoprotein, mmol/L	1.3(0.4);n=593	1.32(0.4);n=67	1.34(0.4);n=526	0.04	1.3(0.4);n=212	1
SD of high-density lipoprotein	0.1(0.1);n=280	0.12(0.09);n=30	0.14(0.14);n=250	0.17	0.2(0.1);n=87	0

Propensity score matching in 1:2 ratio between PD-1 users and PD-L1 users using the nearest neighbor search strategy was used. The results of logistics regression for potential confounders used in propensity score calculations, balance between groups, and estimations of bootstrapped standard error are shown in **Supplementary Tables 3, 4 and 5**, respectively. Distributions of propensity scores before and after matching are shown in **Supplementary Fig. 1**. These results indicate that the covariates between the groups are balanced after matching.

Adverse cardiovascular outcomes on follow-up and their significant predictors

In the matched cohort, 425 (IR: 64.10%) patients died and 91 (IR: 13.72%) developed new onset cardiac composite outcome. Amongst the latter, 75 (IR: 11.31%) developed heart failure, 8 (IR: 1.20%) developed acute myocardial infarction, 8 (IR: 1.20%) developed atrial fibrillation and 2 (IR: 0.30%) developed atrial flutter. The incidence rate of the composite outcome was lower in the PD-L1 cohort than in the PD-1 cohort (7.0% vs. 20.7%; $P < 0.001$).

In the 221 PD-L1 users, there were 11 patients (IR: 4.97%) who developed the composite outcome, in which 10 (IR: 4.52%) with heart failure, 1 (0.45%) with atrial fibrillation, but none with acute myocardial infarction or atrial flutter. In the 442 patients PD-1 users, 80 patients (IR: 18.09%) developed the composite outcome. Of the latter group, 65 (IR: 14.70%) developed heart failure, 8 (IR: 1.80%) developed acute myocardial infarction, 7 (IR: 1.58%) developed atrial fibrillation, and 2 (IR: 0.45%) developed atrial flutter.

The breakdown on the individual adverse events is shown in Fig. 1 and the patient characteristics stratified by adverse cardiovascular outcomes are shown in Table 2 and Table 3. The Kaplan-Meier survival curves and the cumulative incidence curves of new onset cardiac complications and all-cause mortality in cancer patients stratified by PD-1 or PD-L1 inhibitor use before and after 1:2 propensity score matching were presented in Fig. 2 and Fig. 3, respectively. The baseline characteristics of the cohort stratified by mortality status are shown in **Supplementary Table 6**.

Table 2
Clinical characteristics of patients who developed the composite outcome before and after 1:2 propensity score matching

Before matching					After 1:2 matching	
Characteristics	All (N = 1959)	PD-L1 users (N = 221)	PD-1 users (N = 1738)	SMD	All (N = 663)	PD-L1 users (N = 221)
	Mean(SD);N or Count(%)	Mean(SD);N or Count(%)	Mean(SD);N or Count(%)		Mean(SD);N or Count(%)	Mean(SD);N or Count(%)
Adverse events						
All-cause mortality	1319(67.33%)	115(52.03%)	1204(69.27%)	0.36*	425(64.10%)	115(52.03%)
Composite outcome	320(16.33%)	11(4.97%)	309(17.77%)	0.41*	91(13.72%)	11(4.97%)
Heart failure	244(12.45%)	10(4.52%)	234(13.46%)	0.32*	75(11.31%)	10(4.52%)
Acute myocardial infarction	38(1.93%)	0(0.00%)	38(2.18%)	0.21*	8(1.20%)	0(0.00%)
Atrial fibrillation	54(2.75%)	1(0.45%)	53(3.04%)	0.2	8(1.20%)	1(0.45%)
Atrial flutter	6(0.30%)	0(0.00%)	6(0.34%)	0.08	2(0.30%)	0(0.00%)
Demographics						
Male gender	1341(68.45%)	165(74.66%)	1176(67.66%)	0.15	498(75.11%)	165(74.66%)
Female gender	618(31.54%)	56(25.33%)	562(32.33%)	0.15	165(24.88%)	56(25.33%)
Baseline age, years	61.0(13.7);n = 1959	63.1(10.2);n = 221	60.7(14.1);n = 1738	0.19	63.0(10.2);n = 663	63.1(10.2);n = 221
< 40	151(7.70%)	7(3.16%)	144(8.28%)	0.22*	20(3.01%)	7(3.16%)
[40, 50)	194(9.90%)	13(5.88%)	181(10.41%)	0.17	43(6.48%)	13(5.88%)
[50–60)	481(24.55%)	51(23.07%)	430(24.74%)	0.04	155(23.37%)	51(23.07%)
[60–70)	631(32.21%)	96(43.43%)	535(30.78%)	0.26*	288(43.43%)	96(43.43%)
[70–80)	391(19.95%)	48(21.71%)	343(19.73%)	0.05	133(20.06%)	48(21.71%)
>=80	111(5.66%)	6(2.71%)	105(6.04%)	0.16	24(3.61%)	6(2.71%)
Past comorbidities						
Charlson standard comorbidity index	6.1(3.3);n = 1959	6.5(3.1);n = 221	6.0(3.3);n = 1738	0.16	6.5(3.1);n = 663	6.53(3.1);n = 221
Hypertension	256(13.06%)	29(13.12%)	227(13.06%)	0	88(13.27%)	29(13.12%)
Liver diseases	193(9.85%)	8(3.61%)	185(10.64%)	0.28*	24(3.61%)	8(3.61%)
Hip fractures/accident falls	77(3.93%)	13(5.88%)	64(3.68%)	0.1	37(5.58%)	13(5.88%)
Renal diseases	292(14.90%)	29(13.12%)	263(15.13%)	0.06	85(12.82%)	29(13.12%)
Diabetes mellitus	156(7.96%)	20(9.04%)	136(7.82%)	0.04	60(9.04%)	20(9.04%)
Maligt dysrhythmia	12(0.61%)	0(0.00%)	12(0.69%)	0.12	2(0.30%)	0(0.00%)
Chronic obstructive pulmonary disease	15(0.76%)	2(0.90%)	13(0.74%)	0.02	6(0.90%)	2(0.90%)
Ischemic heart disease	61(3.11%)	5(2.26%)	56(3.22%)	0.06	15(2.26%)	5(2.26%)
Peripheral vascular disease	11(0.56%)	1(0.45%)	10(0.57%)	0.02	3(0.45%)	1(0.45%)
Endocrine diseases	548(27.97%)	56(25.33%)	492(28.30%)	0.07	166(25.03%)	56(25.33%)

* for SMD 0.2; # indicates the difference between patients with/without the composite outcome

APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors

	Before matching				After 1:2 matching	
Gastrointestinal diseases	1412(72.07%)	184(83.25%)	1228(70.65%)	0.30*	551(83.10%)	184(83.25%)
Stroke/transient ischemic attack	80(4.08%)	8(3.61%)	72(4.14%)	0.03	24(3.61%)	8(3.61%)
Hospitalization						
Average readmission	68.5(194.8);n = 1876	53.3(112.0);n = 215	70.5(203.0);n = 1661	0.1	65.3(202.3);n = 647	53.3(112.0);n = 215
Total episode number	14.2(13.9);n = 1876	12.2(8.9);n = 215	14.5(14.4);n = 1661	0.19	13.8(10.9);n = 647	12.2(8.9);n = 215
Overall hospital stay, days	35.2(38.2);n = 1876	25.5(22.4);n = 215	36.5(39.6);n = 1661	0.34*	32.9(31.3);n = 647	25.5(22.4);n = 215
Medications						
PD-L1 v.s. PD-1	221(11.28%)	221(100.00%)	0(0.00%)	inf*	221(33.33%)	221(100.00%)
PD-L1 expenditure, HKD	98251.0(98697.8);n = 221	98251.0(98697.8);n = 221	-	-	98251.0(98697.8);n = 221	98251.0(98697.8);n = 221
Total PD-L1 dose amount, mg	12644.1(27488.6);n = 221	12644.1(27488.6);n = 221	-	-	12644.1(27488.6);n = 221	12644.1(27488.6);n = 221
PD-L1 inhibitors duration, days	176.0(200.9);n = 221	176.0(200.9);n = 221	-	-	176.0(200.9);n = 221	176.0(200.9);n = 221
PD-1 expenditure	193878.8(291968.7);n = 1750	333403.4(284147.8);n = 12	192915.5(291869.7);n = 1738	0.49*	203782.5(259059.2);n = 454	333403.4(284147.8);n = 12
Total PD-1 dose amount (MG)	2817.9(10492.2);n = 1750	1450.0(1049.5);n = 12	2827.3(10527.4);n = 1738	0.18	2454.7(5152.0);n = 454	1450.0(1049.5);n = 12
PD-1 inhibitors duration, days	202.7(237.7);n = 1750	383.3(270.7);n = 12	201.5(237.0);n = 1738	0.71*	207.7(234.7);n = 454	383.3(270.7);n = 12
Anticoagulants	1108(56.55%)	120(54.29%)	988(56.84%)	0.05	362(54.60%)	120(54.29%)
Steroids	1108(56.55%)	120(54.29%)	988(56.84%)	0.05	362(54.60%)	120(54.29%)
Inflammatory subclinical biomarkers						
Neutrophil-to-lymphocyte ratio	4.6(6.4);n = 1952	4.5(9.5);n = 221	4.6(5.9);n = 1731	0.01	4.3(6.5);n = 663	4.5(9.5);n = 221
Platelet-to-lymphocyte ratio	212.3(243.9);n = 1953	203.9(188.4);n = 221	213.4(250.1);n = 1732	0.04	210.2(304.3);n = 663	203.9(188.4);n = 221
Aspartate transaminase-to-alanine transaminase ratio	1.8(3.6);n = 1308	1.1(0.5);n = 128	1.9(3.8);n = 1180	0.29*	1.5(2.1);n = 405	1.1(0.5);n = 128
Triglyceride glucose index	7.1(0.6);n = 580	7.07(0.65);n = 67	7.06(0.62);n = 513	0.02	7.0(0.6);n = 207	7.1(0.6);n = 67
Urea-to-creatinine ratio	73.1(40.8);n = 1937	68.3(23.3);n = 221	73.8(42.4);n = 1716	0.16	69.5(29.2);n = 659	68.3(23.3);n = 221
Monocyte-to-lymphocyte ratio	0.4(0.5);n = 1950	0.4(0.5);n = 221	0.5(0.5);n = 1729	0.03	0.4(0.4);n = 662	0.4(0.5);n = 221
Complete blood counts						
Mean corpuscular volume, fL	88.0(8.2);n = 1953	88.4(7.7);n = 221	88.0(8.2);n = 1732	0.06	88.2(7.7);n = 663	88.4(7.7);n = 221
Eosinophil, x10 ⁹ /L	0.2(0.3);n = 1952	0.2(0.32);n = 221	0.18(0.31);n = 1731	0.04	0.2(0.3);n = 663	0.2(0.32);n = 221
Lymphocyte, x10 ⁹ /L	1.5(0.9);n = 1953	1.6(0.8);n = 221	1.5(0.9);n = 1732	0.19	1.5(0.7);n = 663	1.6(0.8);n = 221

* for SMD 0.2; # indicates the difference between patients with/without the composite outcome

APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors

Before matching				After 1:2 matching		
Metamyelocyte, x10 ⁹ /L	0.8(5.0);n = 225	0.5(0.7);n = 13	0.8(5.2);n = 212	0.07	0.3(0.5);n = 72	0.5(0.7);n = 13
Monocyte, x10 ⁹ /L	0.5(0.3);n = 1953	0.54(0.25);n = 221	0.53(0.32);n = 1732	0.02	0.5(0.3);n = 663	0.54(0.25);n = 221
Neutrophil, x10 ⁹ /L	5.1(3.3);n = 1953	5.2(3.4);n = 221	5.0(3.3);n = 1732	0.05	5.0(3.2);n = 663	5.2(3.4);n = 221
White blood count, x10 ⁹ /L	7.4(5.5);n = 1953	7.43(3.3);n = 221	7.39(5.74);n = 1732	0.01	7.3(3.6);n = 663	7.4(3.3);n = 221
Mean cell haemoglobin, pg	30.7(3.3);n = 1953	30.72(3.29);n = 221	30.65(3.34);n = 1732	0.02	30.8(3.2);n = 663	30.7(3.3);n = 221
Myelocyte, x10 ⁹ /L	0.8(3.1);n = 328	1.0(2.0);n = 26	0.7(3.2);n = 302	0.08	0.6(1.5);n = 97	1.0(2.0);n = 26
Platelet, x10 ⁹ /L	247.9(108.5);n = 1953	261.5(92.6);n = 221	246.2(110.3);n = 1732	0.15	252.6(98.9);n = 663	261.5(92.6);n = 221
Red blood count, x10 ¹² /L	4.4(0.7);n = 1953	4.6(0.6);n = 221	4.4(0.7);n = 1732	0.27*	4.5(0.7);n = 663	4.6(0.6);n = 221
Hematocrit, L/L	0.4(0.1);n = 1895	0.4(0.05);n = 208	0.38(0.06);n = 1687	0.37*	0.4(0.1);n = 626	0.4(0.05);n = 208
Renal and liver functions						
K/Potassium, mmol/L	4.1(0.4);n = 1941	4.14(0.43);n = 221	4.12(0.44);n = 1720	0.04	4.1(0.4);n = 661	4.14(0.43);n = 221
Urate, mmol/L	0.3(0.1);n = 627	0.33(0.1);n = 43	0.33(0.14);n = 584	0.03	0.3(0.1);n = 186	0.33(0.1);n = 43
Albumin, g/L	39.2(5.9);n = 1939	39.8(5.4);n = 220	39.1(6.0);n = 1719	0.11	39.5(5.4);n = 660	39.8(5.4);n = 220
Na/Sodium, mmol/L	139.1(3.8);n = 1941	139.4(3.1);n = 221	139.1(3.9);n = 1720	0.09	139.2(3.4);n = 661	139.4(3.1);n = 221
Urea, mmol/L	5.5(2.4);n = 1937	5.3(1.8);n = 221	5.6(2.5);n = 1716	0.11	5.3(1.8);n = 659	5.31(1.76);n = 221
Protein, g/L	72.1(12.8);n = 1853	71.3(16.3);n = 207	72.2(12.3);n = 1646	0.06	71.7(14.4);n = 624	71.3(16.3);n = 207
Bilirubin, umol/L	13.0(25.3);n = 1941	9.5(6.1);n = 221	13.4(26.7);n = 1720	0.2	11.3(19.1);n = 661	9.5(6.1);n = 221
Creatinine, umol/L	84.9(62.4);n = 1952	83.0(37.0);n = 221	85.1(64.9);n = 1731	0.04	84.8(64.0);n = 662	83.0(37.0);n = 221
SD of creatinine	35.5(103.7);n = 1942	29.8(93.9);n = 220	36.2(104.9);n = 1722	0.06	29.7(82.3);n = 658	29.8(93.9);n = 220
Aspartate transaminase, U/L	54.4(104.9);n = 1371	28.3(21.8);n = 142	57.5(110.1);n = 1229	0.37*	41.2(67.2);n = 443	28.3(21.8);n = 142
SD of aspartate transaminase	59.6(189.6);n = 1250	28.6(101.7);n = 122	62.9(196.5);n = 1128	0.22*	36.5(84.3);n = 409	28.6(101.7);n = 122
Alkaline phosphatase, U/L	108.6(111.6);n = 1941	85.2(36.4);n = 221	111.6(117.5);n = 1720	0.3*	102.1(99.9);n = 661	85.2(36.4);n = 221
SD of alkaline phosphatase	64.8(95.1);n = 1928	39.6(75.3);n = 220	68.0(96.9);n = 1708	0.33*	58.3(89.9);n = 655	39.6(75.3);n = 220
Alanine transaminase, U/L	36.6(55.7);n = 1876	28.2(25.1);n = 207	37.6(58.3);n = 1669	0.21*	31.4(29.5);n = 623	28.2(25.1);n = 207
SD of alanine transaminase	36.4(84.7);n = 1855	22.9(50.7);n = 201	38.0(87.8);n = 1654	0.21*	28.2(51.6);n = 612	22.9(50.7);n = 201
Lipid, iron and calcium profile						
Total iron-binding capacity, L	41.0(12.3);n = 103	39.1(11.1);n = 5	41.1(12.4);n = 98	0.16	42.1(12.7);n = 22	39.1(11.1);n = 5
VitaminB12, pmol/L	453.2(327.2);n = 49	447.7(265.6);n = 3	453.6(333.2);n = 46	0.02	401.2(305.7);n = 17	447.7(265.6);n = 3
Folate, ng/mL	21.7(10.2);n = 69	16.0(3.7);n = 3	22.0(10.3);n = 66	0.78*	20.4(10.4);n = 19	16.0(3.7);n = 3
Ferritin, pmol/L	2546.7(4740.6);n = 86	728.2(816.5);n = 8	2733.2(4936.4);n = 78	0.57*	1941.1(2987.1);n = 22	728.2(816.5);n = 8
Calcium, mmol/L	2.3(0.2);n = 1081	2.32(0.13);n = 82	2.32(0.16);n = 999	0.04	2.3(0.1);n = 340	2.32(0.13);n = 82

* for SMD 0.2; # indicates the difference between patients with/without the composite outcome

APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors

	Before matching				After 1:2 matching	
SD of calcium	0.1(0.1);n = 987	0.07(0.04);n = 73	0.1(0.06);n = 914	0.49*	0.1(0.1);n = 314	0.07(0.04);n = 73
Phosphate, mmol/L	1.1(0.2);n = 948	1.08(0.18);n = 61	1.06(0.22);n = 887	0.11	1.1(0.2);n = 286	1.08(0.18);n = 61
SD of phosphate	0.2(0.1);n = 785	0.1(0.1);n = 44	0.2(0.1);n = 741	0.41*	0.2(0.1);n = 241	0.1(0.1);n = 44
Inorganic, mmol/L	6.4(8.7);n = 259	4.1(5.4);n = 24	6.6(8.9);n = 235	0.34*	6.5(10.2);n = 79	4.1(5.4);n = 24
SD of inorganic	2.1(3.5);n = 113	0.5(0.7);n = 13	2.3(3.7);n = 100	0.7*	0.8(1.4);n = 41	0.5(0.7);n = 13
Glycemic and clotting profile						
Triglyceride, mmol/L	1.4(1.1);n = 598	1.5(1.0);n = 68	1.4(1.1);n = 530	0.08	1.5(1.2);n = 214	1.5(1.05);n = 68
SD of triglyceride	0.4(0.5);n = 294	0.4(0.43);n = 30	0.35(0.54);n = 264	0.1	0.4(0.6);n = 90	0.4(0.43);n = 30
Glucose, mmol/L	6.3(2.3);n = 1773	6.4(2.7);n = 206	6.2(2.2);n = 1567	0.09	6.3(2.2);n = 608	6.4(2.7);n = 206
SD of glucose	1.5(1.3);n = 1638	1.4(1.3);n = 194	1.5(1.3);n = 1444	0.09	1.5(1.4);n = 564	1.4(1.3);n = 194
HbA1c, g/dL	12.8(2.0);n = 1953	13.3(1.7);n = 221	12.8(2.0);n = 1732	0.31*	13.1(1.9);n = 663	13.3(1.7);n = 221
SD of HbA1c	1.3(0.5);n = 1947	1.31(0.54);n = 220	1.29(0.54);n = 1727	0.05	1.3(0.5);n = 660	1.31(0.54);n = 220
High sensitive troponin-I, ng/L	363.3(10967.7);n = 1141	12.7(31.8);n = 122	405.3(11605.6);n = 1019	0.05	35.5(314.8);n = 372	12.7(31.8);n = 122
SD of high sensitive troponin-I	124.0(1328.2);n = 755	18.2(42.4);n = 82	136.9(1406.3);n = 673	0.12	34.7(207.0);n = 245	18.2(42.4);n = 82
APTT, second	30.8(5.5);n = 694	29.1(3.5);n = 46	30.9(5.6);n = 648	0.39*	30.4(3.9);n = 217	29.1(3.5);n = 46
SD of APTT	2.6(3.1);n = 510	1.9(2.3);n = 26	2.6(3.2);n = 484	0.28*	2.1(1.8);n = 152	1.9(2.3);n = 26
Lactate dehydrogenase, U/L	324.1(422.0);n = 1431	315.6(534.6);n = 145	325.1(407.6);n = 1286	0.02	302.1(354.0);n = 466	315.6(534.6);n = 145
SD of lactate dehydrogenase	155.2(397.1);n = 1140	115.6(203.9);n = 102	159.1(411.1);n = 1038	0.13	121.3(206.3);n = 365	115.6(203.9);n = 102
Total cholesterol, mmol/L	4.6(1.1);n = 599	4.9(1.0);n = 68	4.5(1.1);n = 531	0.29*	4.6(1.1);n = 214	4.9(1.0);n = 68
SD of total cholesterol	0.5(0.4);n = 295	0.54(0.43);n = 31	0.48(0.44);n = 264	0.14	0.5(0.5);n = 93	0.54(0.43);n = 31
Low-density lipoprotein, mmol/L	2.6(0.9);n = 583	2.9(0.9);n = 65	2.6(0.9);n = 518	0.34*	2.7(1.0);n = 208	2.9(0.9);n = 65
SD of low-density lipoprotein	0.4(0.4);n = 283	0.5(0.4);n = 29	0.4(0.4);n = 254	0.18	0.4(0.4);n = 88	0.5(0.4);n = 29
High-density lipoprotein, mmol/L	1.3(0.4);n = 593	1.32(0.4);n = 67	1.34(0.4);n = 526	0.04	1.3(0.4);n = 212	1.32(0.4);n = 67
SD of high-density lipoprotein	0.1(0.1);n = 280	0.12(0.09);n = 30	0.14(0.14);n = 250	0.17	0.2(0.1);n = 87	0.1(0.1);n = 30
* for <i>SMD</i> 0.2; # indicates the difference between patients with/without the composite outcome						
APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors						

Table 3

Significant univariate predictors of new onset cardiac complication outcome and all-cause mortality before and after 1:2 propensity score matching

Characteristics	Before matching		SMD	After 1:2 matching		SMD
	Composite outcome (N = 320) Mean(SD);N or Count(%)	No composite outcome (N = 1639) Mean(SD);N or Count(%)		Composite outcome (N = 91) Mean(SD);N or Count(%)	No composite outcome (N = 572) Mean(SD);N or Count(%)	
Demographics						
Male gender	219(68.43%)	1122(68.45%)	< 0.01	69(75.82%)	429(75.00%)	0.02
Female gender	101(31.56%)	517(31.54%)	< 0.01	22(24.17%)	143(25.00%)	0.02
Baseline age, years	64.0(12.8);n = 320	60.4(13.8);n = 1639	0.27*	62.7(10.3);n = 91	63.1(10.1);n = 572	0.04
< 40	16(5.00%)	135(8.23%)	0.13	4(4.39%)	16(2.79%)	0.09
[40, 50)	24(7.50%)	170(10.37%)	0.1	6(6.59%)	37(6.46%)	0.01
[50–60)	70(21.87%)	411(25.07%)	0.08	24(26.37%)	131(22.90%)	0.08
[60–70)	106(33.12%)	525(32.03%)	0.02	36(39.56%)	252(44.05%)	0.09
[70–80)	74(23.12%)	317(19.34%)	0.09	17(18.68%)	116(20.27%)	0.04
>=80	30(9.37%)	81(4.94%)	0.17	4(4.39%)	20(3.49%)	0.05
Past comorbidities						
Charlson standard comorbidity index	6.7(3.3);n = 320	6.0(3.3);n = 1639	0.23*	7.0(3.1);n = 91	6.4(3.1);n = 572	0.18
Hypertension	49(15.31%)	207(12.62%)	0.08	13(14.28%)	75(13.11%)	0.03
Liver diseases	22(6.87%)	171(10.43%)	0.13	3(3.29%)	21(3.67%)	0.02
Hip fractures/accident falls	19(5.93%)	58(3.53%)	0.11	9(9.89%)	28(4.89%)	0.19
Renal diseases	55(17.18%)	237(14.46%)	0.07	12(13.18%)	73(12.76%)	0.01
Diabetes mellitus	30(9.37%)	126(7.68%)	0.06	10(10.98%)	50(8.74%)	0.08
Maligt dysrhythmia	10(3.12%)	2(0.12%)	0.24*	0(0.00%)	2(0.34%)	0.08
Chronic obstructive pulmonary disease	3(0.93%)	12(0.73%)	0.02	2(2.19%)	4(0.69%)	0.13
Ischemic heart disease	19(5.93%)	42(2.56%)	0.17	3(3.29%)	12(2.09%)	0.07
Peripheral vascular disease	3(0.93%)	8(0.48%)	0.05	1(1.09%)	2(0.34%)	0.09
Endocrine diseases	76(23.75%)	472(28.79%)	0.11	20(21.97%)	146(25.52%)	0.08
Gastrointestinal diseases	230(71.87%)	1182(72.11%)	0.01	82(90.10%)	469(81.99%)	0.24*
Stroke/transient ischemic attack	17(5.31%)	63(3.84%)	0.07	3(3.29%)	21(3.67%)	0.02
Hospitalization						
Average readmission	45.2(87.1);n = 312	73.1(209.5);n = 1564	0.17	31.0(35.6);n = 90	70.9(217.1);n = 557	0.26*
Total episode number	13.2(11.4);n = 312	14.4(14.4);n = 1564	0.09	14.5(9.0);n = 90	13.7(11.1);n = 557	0.08
Overall hospital stay, days	40.4(38.3);n = 312	34.2(38.1);n = 1564	0.16	44.7(34.7);n = 90	31.0(30.4);n = 557	0.42*
Medications						
PD-L1 v.s. PD-1	11(3.43%)	210(12.81%)	0.35*	11(12.08%)	210(36.71%)	0.60*
PD-L1 expenditure, HKD	58752.6(47219.8);n = 11	100319.9(100303.8);n = 210	0.53*	58752.6(47219.8);n = 11	100319.9(100303.8);n = 210	0.53*
Total PD-L1 dose amount, mg	5127.3(4650.4);n = 11	13037.9(28128.8);n = 210	0.39*	5127.3(4650.4);n = 11	13037.9(28128.8);n = 210	0.39*

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$; APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors; CI: Confidence interval; HR: Hazard ratio.

Characteristics	Before matching		SMD	After 1:2 matching		SMD
	Composite outcome (N = 320) Mean(SD);N or Count(%)	No composite outcome (N = 1639) Mean(SD);N or Count(%)		Composite outcome (N = 91) Mean(SD);N or Count(%)	No composite outcome (N = 572) Mean(SD);N or Count(%)	
PD-L1 inhibitors duration, days	84.6(114.7);n = 11	180.7(203.5);n = 210	0.58*	84.6(114.7);n = 11	180.7(203.5);n = 210	0.58*
PD-1 expenditure	163440.0(284113.0);n = 309	200406.0(293311.2);n = 1441	0.13	183754.8(224766.1);n = 80	208066.4(265897.1);n = 374	0.1
Total PD-1 dose amount (MG)	5146.2(21240.1);n = 309	2318.6(5983.5);n = 1441	0.18	3948.7(9243.4);n = 80	2135.1(3682.3);n = 374	0.26*
PD-1 inhibitors duration, days	172.1(197.1);n = 309	209.3(245.1);n = 1441	0.17	173.9(197.7);n = 80	214.9(241.5);n = 374	0.19
Anticoagulants	171(53.43%)	937(57.16%)	0.08	47(51.64%)	315(55.06%)	0.07
Steroids	171(53.43%)	937(57.16%)	0.08	47(51.64%)	315(55.06%)	0.07
Inflammatory subclinical biomarkers						
Neutrophil-to-lymphocyte ratio	4.3(6.8);n = 320	4.6(6.3);n = 1632	0.05	3.5(1.8);n = 91	4.4(6.9);n = 572	0.19
Platelet-to-lymphocyte ratio	209.3(237.5);n = 320	212.9(245.2);n = 1633	0.02	199.9(135.5);n = 91	211.8(323.2);n = 572	0.05
Aspartate transaminase-to-alanine transaminase ratio	1.7(1.7);n = 204	1.8(3.9);n = 1104	0.05	1.2(0.6);n = 52	1.5(2.2);n = 353	0.2
Triglyceride glucose index	6.9(0.5);n = 106	7.1(0.6);n = 474	0.35*	6.8(0.5);n = 28	7.1(0.6);n = 179	0.44*
Urea-to-creatinine ratio	72.9(30.7);n = 317	73.2(42.5);n = 1620	0.01	78.0(45.9);n = 91	68.1(25.3);n = 568	0.26*
Monocyte-to-lymphocyte ratio	0.4(0.4);n = 319	0.5(0.5);n = 1631	0.05	0.44(0.36);n = 90	0.45(0.45);n = 572	0.03
Complete blood counts						
Mean corpuscular volume, fL	88.9(7.8);n = 320	87.8(8.2);n = 1633	0.13	89.9(5.1);n = 91	87.9(8.0);n = 572	0.29*
Eosinophil, x10 ⁹ /L	0.18(0.2);n = 320	0.19(0.33);n = 1632	0.02	0.21(0.21);n = 91	0.2(0.27);n = 572	0.05
Lymphocyte, x10 ⁹ /L	1.6(1.0);n = 320	1.5(0.9);n = 1633	0.08	1.6(0.6);n = 91	1.5(0.7);n = 572	0.09
Metamyelocyte, x10 ⁹ /L	0.3(0.6);n = 37	0.9(5.5);n = 188	0.13	0.35(0.36);n = 11	0.34(0.53);n = 61	0.02
Monocyte, x10 ⁹ /L	0.54(0.3);n = 320	0.53(0.31);n = 1633	0.02	0.6(0.4);n = 91	0.5(0.3);n = 572	0.1
Neutrophil, x10 ⁹ /L	5.0(3.2);n = 320	5.1(3.3);n = 1633	0.02	4.99(2.76);n = 91	5.02(3.28);n = 572	0.01
White blood count, x10 ⁹ /L	7.41(3.71);n = 320	7.39(5.8);n = 1633	0	7.4(3.2);n = 91	7.3(3.7);n = 572	0.01
Mean cell haemoglobin, pg	30.9(3.2);n = 320	30.6(3.4);n = 1633	0.08	31.4(2.4);n = 91	30.7(3.3);n = 572	0.24*
Myelocyte, x10 ⁹ /L	0.5(0.9);n = 50	0.8(3.3);n = 278	0.14	0.4(0.5);n = 16	0.7(1.6);n = 81	0.27*
Platelet, x10 ⁹ /L	248.7(100.8);n = 320	247.8(110.0);n = 1633	0.01	258.9(81.8);n = 91	251.6(101.4);n = 572	0.08
Red blood count, x10 ¹² /L	4.36(0.68);n = 320	4.4(0.71);n = 1633	0.06	4.54(0.51);n = 91	4.45(0.68);n = 572	0.14
Hematocrit, L/L	0.38(0.05);n = 303	0.38(0.06);n = 1592	0.02	0.41(0.04);n = 79	0.39(0.05);n = 547	0.39*
Renal and liver functions						
K/Potassium, mmol/L	4.14(0.45);n = 318	4.12(0.43);n = 1623	0.03	4.12(0.39);n = 91	4.13(0.43);n = 570	0.02
Urate, mmol/L	0.34(0.17);n = 96	0.32(0.13);n = 531	0.14	0.33(0.19);n = 32	0.34(0.11);n = 154	0.02
Albumin, g/L	39.17(5.99);n = 318	39.2(5.89);n = 1621	0	40.4(4.3);n = 91	39.4(5.6);n = 569	0.21*

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$; APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors; CI: Confidence interval; HR: Hazard ratio.

Characteristics	Before matching		SMD	After 1:2 matching		SMD
	Composite outcome (N = 320) Mean(SD);N or Count(%)	No composite outcome (N = 1639) Mean(SD);N or Count(%)		Composite outcome (N = 91) Mean(SD);N or Count(%)	No composite outcome (N = 572) Mean(SD);N or Count(%)	
Na/Sodium, mmol/L	139.0(3.8);n = 318	139.1(3.8);n = 1623	0.03	139.2(3.6);n = 91	139.3(3.4);n = 570	0.01
Urea, mmol/L	5.7(2.8);n = 317	5.5(2.4);n = 1620	0.08	5.34(2.09);n = 91	5.3(1.76);n = 568	0.02
Protein, g/L	72.6(12.5);n = 308	72.0(12.9);n = 1545	0.04	72.2(12.5);n = 87	71.6(14.7);n = 537	0.05
Bilirubin, umol/L	11.9(16.6);n = 318	13.2(26.6);n = 1623	0.05	10.9(7.3);n = 91	11.4(20.3);n = 570	0.04
Creatinine, umol/L	84.6(44.3);n = 320	85.0(65.3);n = 1632	0.01	78.0(42.3);n = 91	85.9(66.8);n = 571	0.14
SD of creatinine	39.6(128.3);n = 319	34.7(98.1);n = 1623	0.04	28.8(55.2);n = 91	29.9(85.9);n = 567	0.01
Aspartate transaminase, U/L	45.2(56.6);n = 221	56.2(111.7);n = 1150	0.12	29.0(15.0);n = 64	43.3(72.3);n = 379	0.27*
SD of aspartate transaminase	57.8(157.0);n = 198	59.9(195.2);n = 1052	0.01	30.5(74.7);n = 62	37.5(85.9);n = 347	0.09
Alkaline phosphatase, U/L	98.9(76.8);n = 318	110.5(117.1);n = 1623	0.12	87.6(42.5);n = 91	104.4(106.1);n = 570	0.21*
SD of alkaline phosphatase	68.8(96.7);n = 317	64.0(94.8);n = 1611	0.05	62.9(90.6);n = 90	57.5(89.9);n = 565	0.06
Alanine transaminase, U/L	36.0(69.2);n = 301	36.7(52.8);n = 1575	0.01	26.7(16.3);n = 79	32.1(30.9);n = 544	0.22*
SD of alanine transaminase	40.6(122.4);n = 300	35.6(75.3);n = 1555	0.05	21.6(21.1);n = 78	29.2(54.6);n = 534	0.18
Lipid, iron and calcium profile						
Total iron-binding capacity, L	41.4(14.2);n = 13	40.9(12.1);n = 90	0.04	61.3(15.3);n = 2	40.2(11.1);n = 20	1.58*
VitaminB12, pmol/L	305.1(109.5);n = 6	473.9(342.5);n = 43	0.66*	304.0(145.7);n = 2	414.1(322.1);n = 15	0.44*
Folate, ng/mL	26.5(14.2);n = 8	21.1(9.5);n = 61	0.44*	32.3(29.6);n = 2	19.0(6.8);n = 17	0.62*
Ferritin, pmol/L	3257.7(4708.7);n = 12	2431.4(4767.6);n = 74	0.17	5116.7(6053.8);n = 2	1623.6(2601.0);n = 20	0.75*
Calcium, mmol/L	2.31(0.14);n = 185	2.32(0.16);n = 896	0.06	2.34(0.1);n = 53	2.32(0.15);n = 287	0.1
SD of calcium	0.09(0.06);n = 167	0.1(0.06);n = 820	0.05	0.09(0.06);n = 48	0.09(0.07);n = 266	0.01
Phosphate, mmol/L	1.0(0.2);n = 159	1.1(0.2);n = 789	0.05	1.0(0.2);n = 41	1.1(0.2);n = 245	0.09
SD of phosphate	0.17(0.12);n = 122	0.16(0.11);n = 663	0.05	0.17(0.12);n = 33	0.15(0.09);n = 208	0.16
Inorganic, mmol/L	4.8(5.7);n = 36	6.7(9.0);n = 223	0.24*	3.5(5.4);n = 8	6.9(10.5);n = 71	0.41*
SD of inorganic	2.4(3.8);n = 17	2.1(3.5);n = 96	0.1	0.2(0.1);n = 6	0.9(1.5);n = 35	0.69*
Glycemic and clotting profile						
Triglyceride, mmol/L	1.2(0.8);n = 110	1.5(1.1);n = 488	0.24*	1.1(0.7);n = 30	1.5(1.3);n = 184	0.38*
SD of triglyceride	0.3(0.4);n = 46	0.4(0.5);n = 248	0.23*	0.3(0.2);n = 8	0.4(0.6);n = 82	0.28*
Glucose, mmol/L	6.2(2.1);n = 294	6.3(2.3);n = 1479	0.03	6.1(1.5);n = 86	6.3(2.3);n = 522	0.13
SD of glucose	1.55(1.26);n = 276	1.48(1.3);n = 1362	0.05	1.6(1.4);n = 83	1.5(1.4);n = 481	0.1
HbA1c, g/dL	12.9(1.9);n = 320	12.8(2.0);n = 1633	0.03	13.6(1.5);n = 91	13.0(1.9);n = 572	0.35*
SD of HbA1c	1.4(0.5);n = 320	1.3(0.6);n = 1627	0.14	1.5(0.4);n = 91	1.3(0.5);n = 569	0.41*
High sensitive troponin-I, ng/L	1660.7(24305.4);n = 232	32.2(442.8);n = 909	0.09	106.2(718.1);n = 70	19.1(50.2);n = 302	0.17
SD of high sensitive troponin-I	367.5(2445.0);n = 164	56.5(762.9);n = 591	0.17	101.3(453.4);n = 48	18.5(51.9);n = 197	0.26*
APTT, second	30.4(4.2);n = 118	30.9(5.8);n = 576	0.09	30.36(3.19);n = 34	30.44(3.98);n = 183	0.02

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$; APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors; CI: Confidence interval; HR: Hazard ratio.

Characteristics	Before matching		SMD	After 1:2 matching		SMD
	Composite outcome (N = 320) Mean(SD);N or Count(%)	No composite outcome (N = 1639) Mean(SD);N or Count(%)		Composite outcome (N = 91) Mean(SD);N or Count(%)	No composite outcome (N = 572) Mean(SD);N or Count(%)	
SD of APTT	2.1(1.6);n = 79	2.7(3.3);n = 431	0.24*	2.0(1.7);n = 22	2.1(1.8);n = 130	0.02
Lactate dehydrogenase, U/L	326.8(437.7);n = 247	323.6(418.8);n = 1184	0.01	273.8(128.9);n = 72	307.3(380.9);n = 394	0.12
SD of lactate dehydrogenase	133.2(228.0);n = 182	159.3(421.6);n = 958	0.08	131.0(187.3);n = 57	119.5(209.9);n = 308	0.06
Total cholesterol, mmol/L	4.4(1.0);n = 110	4.6(1.1);n = 489	0.18	4.9(1.4);n = 30	4.6(1.0);n = 184	0.24*
SD of total cholesterol	0.4(0.4);n = 46	0.5(0.4);n = 249	0.15	0.7(0.9);n = 8	0.5(0.4);n = 85	0.32*
Low-density lipoprotein, mmol/L	2.5(0.9);n = 109	2.6(0.9);n = 474	0.13	3.0(1.3);n = 30	2.6(0.9);n = 178	0.3*
SD of low-density lipoprotein	0.38(0.35);n = 44	0.42(0.37);n = 239	0.11	0.7(0.8);n = 8	0.4(0.3);n = 80	0.45*
High-density lipoprotein, mmol/L	1.4(0.4);n = 109	1.3(0.4);n = 484	0.07	1.4(0.3);n = 30	1.3(0.4);n = 182	0.26*
SD of high-density lipoprotein	0.14(0.13);n = 42	0.14(0.13);n = 238	0.02	0.1(0.1);n = 8	0.2(0.1);n = 79	0.02
* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$; APTT: applied partial thromboplastin test; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors; CI: Confidence interval; HR: Hazard ratio.						

Univariate Cox regression identified significant predictors of the primary composite outcome and all-cause mortality before and after propensity score matching (Table 3). Compared with PD-1 inhibitor treatment, PD-L1 inhibitor treatment was significantly associated with a lower risk of composite outcome both before (hazard ratio [HR]: 0.32, 95% CI: [0.18–0.59], P value = 0.0002***) and after matching (HR: 0.34, 95% CI: [0.18–0.65], P value = 0.001**), and lower all-cause mortality risk before matching (HR: 0.77, 95% CI: [0.64–0.93], P value = 0.0078**) and after matching (HR: 0.80, 95% CI: [0.65–1.00], P value = 0.0463).

More PD-L1 expenditure (HR:1.000; 95% CI: 1.000–1.000; P value = 0.0528), shorter PD-L1 inhibitors duration (HR:0.99; 95% CI: 0.99–1.00; P value = 0.0263*), more PD-1 expenditure (HR:1.000; 95% CI: 1.000–1.001; P value = 0.0018**), and shorter PD-1 inhibitors duration (HR:0.998; 95% CI: 0.997–0.999; P value = 0.0007***) were associated with new onset cardiac composite outcome in the matched cohort. Significant laboratory examinations significantly associated with new onset cardiac composite outcome include higher levels of mean corpuscular volume (HR:1.03; 95% CI: 1.00–1.07; P value = 0.0470*), hematocrit (HR:566.25; 95% CI: 4.88–65751.46; P value = 0.0090**), HbA1c (HR:1.19; 95% CI: 1.05–1.34; P value = 0.0072**), total cholesterol (HR:1.42; 95% CI: 1.00–2.00; P value = 0.0490*), and low-density lipoprotein (HR:1.67; 95% CI: 1.14–2.45; P value = 0.0091**).

In addition, greater variability in laboratory tests, including the standard deviations (SD) of alkaline phosphatase (HR:1.002; 95% CI: 1.000–1.004; P value = 0.0359*), HbA1c (HR:1.94; 95% CI: 1.36–2.76; P value = 0.0003***), lactate dehydrogenase (HR:1.002; 95% CI: 1.000–1.003; P value = 0.0056**), and low-density lipoprotein (HR:7.64; 95% CI: 1.84–31.77; P value = 0.0051**) were significantly associated with the composite outcome. The boxplots of significant measures of variability stratified by PD-1/PD-L1 inhibitor treatment in the matched cohort are shown in Fig. 5.

Healthcare utilization before and after treatment with PD-1/PD-L1 inhibitors

Longer overall cumulative hospital stay (HR:1.01; 95% CI: 1.00–1.01; P value = 0.0040**) and longer hospital stay after PD-1/PD-L1 drug use (HR:1.01; 95% CI: 1.00–1.01; P value = 0.0040**) were significantly associated with the composite outcome. Furthermore, hospitalization characteristics before and after PD-1/PD-L1 treatment were compared in the subset of patients who developed the adverse outcomes, in both the unmatched and matched cohorts (Table 4). Patients who developed cardiovascular complications had a shorter average readmission interval, a higher number of hospitalizations and a longer duration of hospital stay after PD-1/PD-L1 treatment ($P < 0.0001$).

Table 4
Comparisons of hospitalization characteristics before and after PD1/PD-L1 treatment in patients with new onset heart failure, acute myocardial infarction, atrial fibrillation, and atrial flutter

Characteristics	Before matching		After 1:2 matching	
	All-cause mortality	Composite outcome	All-cause mortality	Composite outcome
	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value
Demographics				
Male gender	0.98[0.87–1.10];0.6878	1.00[0.78–1.29];0.9898	1.03[0.83–1.29];0.7733	1.12[0.67–1.88];0.6546
Female gender	1.0[Reference]	1.0[Reference]	1.0[Reference]	1.0[Reference]
Baseline age, years	1.00[1.00-1.01];0.1533	1.01[1.01–1.02];0.0016**	1.01[1.00-1.01];0.2976	1.00[0.98–1.02];0.9421
< 40	1.0[Reference]	1.0[Reference]	1.0[Reference]	1.0[Reference]
[40, 50)	1.02[0.85–1.22];0.8400	0.72[0.46–1.12];0.1450	1.07[0.73–1.56];0.7308	0.96[0.39–2.38];0.9321
[50–60)	1.04[0.92–1.18];0.5569	0.97[0.74–1.28];0.8386	0.87[0.69–1.09];0.2345	1.20[0.74–1.95];0.4528
[60–70)	1.02[0.91–1.14];0.7455	1.05[0.82–1.35];0.6880	0.98[0.81–1.19];0.8684	0.71[0.45–1.11];0.1309
[70–80)	0.98[0.85–1.12];0.7150	1.19[0.91–1.57];0.2103	1.16[0.92–1.47];0.2172	1.13[0.66–1.96];0.6528
>=80	1.07[0.86–1.35];0.5366	1.40[0.89–2.21];0.1436	1.03[0.63–1.70];0.9074	1.51[0.55–4.13];0.4210
Past comorbidities				
Charlson standard comorbidity index	1.05[1.04–1.07];<0.0001***	1.08[1.04–1.12];<0.0001***	1.08[1.04–1.11];<0.0001***	1.07[1.00-1.15];0.0589
Hypertension	1.20[1.02–1.40];0.0262*	1.11[0.78–1.59];0.5645	1.32[1.00-1.73];0.0481*	1.18[0.61–2.29];0.6236
Liver diseases	1.24[1.04–1.47];0.0163*	0.77[0.49–1.22];0.2689	1.46[0.91–2.35];0.1148	1.32[0.42–4.18];0.6381
Hip fractures/accident falls	1.26[0.96–1.64];0.0910	1.98[1.21–3.23];0.0065**	0.79[0.50–1.25];0.3174	2.21[1.10–4.41];0.0253*
Renal diseases	1.02[0.88–1.19];0.7670	1.06[0.77–1.48];0.7155	1.05[0.79–1.39];0.7571	1.24[0.67–2.29];0.4871
Diabetes mellitus	1.13[0.92–1.37];0.2369	1.05[0.67–1.66];0.8204	1.12[0.80–1.57];0.4963	1.12[0.52–2.43];0.7733
Maligt dysrhythmia	2.09[1.12–3.89];0.0206*	11.11[5.88–20.98];<0.0001***	0.00[0.00-Inf];0.9877	0.00[0.00-Inf];0.9946
Chronic obstructive pulmonary disease	1.42[0.78–2.56];0.2515	1.83[0.59–5.72];0.2971	2.04[0.84–4.94];0.1133	5.51[1.34–22.64];0.0179*
Ischemic heart disease	0.98[0.72–1.34];0.8984	1.30[0.69–2.44];0.4160	0.98[0.49–1.98];0.9639	0.70[0.10–5.07];0.7271
Peripheral vascular disease	1.10[0.57–2.12];0.7774	1.93[0.62–6.03];0.2570	0.87[0.22–3.51];0.8502	2.51[0.35–18.07];0.3611
Endocrine diseases	1.04[0.93–1.18];0.4907	0.76[0.58-1.00];0.0538	1.04[0.84–1.29];0.7304	0.75[0.44–1.28];0.2934
Gastrointestinal diseases	1.03[0.92–1.17];0.5810	0.94[0.73–1.21];0.6327	1.22[0.93–1.59];0.1534	1.71[0.85–3.41];0.1296
Stroke/transient ischemic attack	1.11[0.85–1.46];0.4279	1.02[0.54–1.92];0.9477	1.48[0.91–2.40];0.1149	0.96[0.24–3.92];0.9586
Hospitalization				
Average readmission	1.000[1.000–1.000];0.2724	0.998[0.997-1.000];0.0625	1.000[1.000-1.001];0.0823	0.99[0.98-1.00];0.0080**
Total episode number	0.95[0.95–0.96];<0.0001***	0.96[0.95–0.97];<0.0001***	0.96[0.95–0.97];<0.0001***	0.97[0.95–0.99];0.0050**
Overall hospital stay, days	1.001[0.999–1.002];0.3779	1.001[0.999–1.004];0.3117	1.00[1.00-1.01];0.0004***	1.01[1.00-1.01];0.0040**
Medications				
PD-L1 v.s. PD-1	0.77[0.64–0.93];0.0078**	0.32[0.18–0.59];0.0002***	0.80[0.65-1.00];0.0463*	0.34[0.18–0.65];0.0010**
PD-L1 expenditure, HKD	1.000[1.000–1.000];<0.0001***	1.000[1.000–1.000];0.0528	1.000[1.000–1.000];<0.0001***	1.000[1.000–1.000];0.0528
Total PD-L1 dose amount, mg	1.000[1.000–1.000];0.0703	1.000[1.000–1.000];0.2410	1.000[1.000–1.000];0.0703	1.000[1.000–1.000];0.2410

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors.

Characteristics	Before matching		After 1:2 matching	
	All-cause mortality	Composite outcome	All-cause mortality	Composite outcome
	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value
PD-L1 inhibitors duration, days	1.00[0.99-1.00]; <0.0001***	0.99[0.99-1.00];0.0263*	1.00[0.99-1.00]; <0.0001***	0.99[0.99-1.00];0.0263*
PD-1 expenditure	1.000[1.000–1.000]; <0.0001***	1.000[1.000–1.000]; <0.0001***	1.000[1.000–1.000]; <0.0001***	1.000[1.000–1.001];0.0018**
Total PD-1 dose amount (MG)	1.000[1.000–1.000]; <0.0001***	1.000[1.000–1.000];0.1842	1.000[1.000–1.000];0.0008***	1.000[1.000–1.000];0.0958
PD-1 inhibitors duration, days	0.997[0.997–0.998]; <0.0001***	0.998[0.997–0.998]; <0.0001***	0.998[0.997–0.998]; <0.0001***	0.998[0.997–0.999];0.0007***
Anticoagulants	0.81[0.73–0.91];0.0002***	0.73[0.58–0.93];0.0097**	0.89[0.74–1.08];0.2423	0.78[0.50–1.20];0.2574
Steroids	0.81[0.73–0.91];0.0002***	0.73[0.58–0.93];0.0097**	0.89[0.74–1.08];0.2423	0.78[0.50–1.20];0.2574
Inflammatory subclinical biomarkers				
Neutrophil-to-lymphocyte ratio	1.01[1.00-1.01];0.0296*	1.00[0.98–1.02];0.8231	1.01[1.00-1.02];0.1025	0.97[0.92–1.03];0.3646
Platelet-to-lymphocyte ratio	1.000[1.000–1.000];0.0261*	1.000[1.000-1.001];0.5907	1.000[1.000–1.000];0.1087	1.000[0.999–1.001];0.9257
Aspartate transaminase-to-alanine transaminase ratio	1.03[1.01–1.04]; <0.0001***	1.01[0.97–1.06];0.6492	1.09[1.04–1.14];0.0004***	0.96[0.71–1.29];0.7683
Triglyceride glucose index	0.97[0.83–1.13];0.6770	0.59[0.41–0.85];0.0040**	0.85[0.66–1.09];0.2061	0.55[0.30–1.02];0.0594
Urea-to-creatinine ratio	1.000[0.999–1.001];0.9657	1.000[0.997–1.002];0.9081	1.00[1.00-1.01];0.2003	1.01[1.00-1.01];0.0007***
Monocyte-to-lymphocyte ratio	1.07[0.99–1.16];0.0998	0.99[0.79–1.23];0.9303	1.20[1.02–1.43];0.0305*	1.07[0.69–1.67];0.7559
Complete blood counts				
Mean corpuscular volume, fL	1.00[0.99–1.01];0.9942	1.01[1.00-1.03];0.1496	1.00[0.98–1.01];0.5845	1.03[1.00-1.07];0.0470*
Eosinophil, x10 ⁹ /L	0.74[0.58–0.93];0.0105*	0.84[0.54–1.31];0.4333	0.81[0.53–1.23];0.3143	1.14[0.49–2.64];0.7632
Lymphocyte, x10 ⁹ /L	0.98[0.92–1.05];0.6221	1.08[0.97–1.20];0.1514	0.96[0.83–1.10];0.5296	1.07[0.78–1.47];0.6699
Metamyelocyte, x10 ⁹ /L	0.87[0.70–1.07];0.1830	0.78[0.46–1.31];0.3392	0.71[0.40–1.28];0.2549	0.74[0.21–2.63];0.6383
Monocyte, x10 ⁹ /L	1.24[1.06–1.45];0.0078**	1.23[0.87–1.73];0.2362	1.51[1.14-2.00];0.0045**	1.65[0.88–3.11];0.1194
Neutrophil, x10 ⁹ /L	1.02[1.01–1.04];0.0013**	1.01[0.98–1.05];0.4025	1.03[1.01–1.06];0.0129*	1.02[0.96–1.08];0.5817
White blood count, x10 ⁹ /L	1.02[1.01–1.03]; <0.0001***	1.02[1.00-1.05];0.1069	1.03[1.00-1.05];0.0187*	1.02[0.97–1.08];0.4938
Mean cell haemoglobin, pg	0.99[0.97–1.01];0.2267	1.01[0.97–1.05];0.6190	0.96[0.94–0.99];0.0133*	1.05[0.97–1.14];0.1981
Myelocyte, x10 ⁹ /L	0.93[0.84–1.02];0.1131	0.88[0.66–1.18];0.3893	0.83[0.66–1.04];0.1098	0.83[0.50–1.39];0.4823
Platelet, x10 ⁹ /L	1.001[1.000-1.001];0.0388*	1.001[1.000-1.002];0.2819	1.002[1.001–1.003];0.0015**	1.002[0.999–1.004];0.1452
Red blood count, x10 ¹² /L	0.93[0.86–1.01];0.0818	0.93[0.78–1.10];0.3688	0.91[0.79–1.06];0.2409	1.26[0.89–1.78];0.1925
Hematocrit, L/L	0.30[0.11–0.80];0.0163*	0.75[0.09–6.67];0.7997	0.18[0.03–1.13];0.0671	566.25[4.88-65751.46];0.0090**
Renal and liver functions				
* for p ≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors.				

Characteristics	Before matching		After 1:2 matching	
	All-cause mortality	Composite outcome	All-cause mortality	Composite outcome
	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value
K/Potassium, mmol/L	0.91[0.80–1.03];0.1211	1.03[0.79–1.35];0.8120	0.87[0.69–1.09];0.2157	0.92[0.56–1.52];0.7440
Urate, mmol/L	1.54[0.72–3.30];0.2671	5.04[0.95–26.62];0.0570	1.71[0.32–9.18];0.5314	0.65[0.02–19.52];0.8040
Albumin, g/L	0.97[0.96–0.98];<0.0001***	0.98[0.96–1.00];0.0540	0.98[0.96–0.99];0.0061**	1.04[0.99–1.09];0.1011
Na/Sodium, mmol/L	0.97[0.96–0.98];<0.0001***	0.97[0.95–1.00];0.0227*	0.95[0.92–0.97];0.0001***	0.97[0.91–1.05];0.4786
Urea, mmol/L	0.99[0.97–1.02];0.5540	1.02[0.98–1.06];0.4164	0.98[0.93–1.03];0.4672	1.00[0.89–1.13];0.9939
Protein, g/L	0.99[0.99–1.00];0.0001***	1.00[0.99–1.01];0.8901	0.99[0.99–1.00];0.0087**	1.00[0.98–1.02];0.9227
Bilirubin, umol/L	1.003[1.002–1.005];<0.0001***	1.00[1.00–1.01];0.5730	1.00[1.00–1.01];0.9330	1.00[0.99–1.01];0.9730
Creatinine, umol/L	1.001[1.000–1.001];0.2210	1.000[0.998–1.002];0.7707	1.001[0.999–1.002];0.2969	1.00[0.99–1.00];0.4195
SD of creatinine	1.001[1.000–1.001];0.0001***	1.001[1.000–1.002];0.0719	1.001[1.000–1.001];0.0974	1.000[0.998–1.002];0.7760
Aspartate transaminase, U/L	1.001[1.001–1.001];<0.0001***	1.000[0.998–1.002];0.8846	1.001[0.999–1.002];0.4383	0.99[0.98–1.01];0.2798
SD of aspartate transaminase	1.001[1.000–1.001];<0.0001***	1.000[1.000–1.001];0.2117	1.001[1.000–1.002];0.0155*	1.001[0.997–1.004];0.6500
Alkaline phosphatase, U/L	1.001[1.001–1.002];<0.0001***	1.000[0.999–1.002];0.7097	1.000[0.999–1.001];0.4551	1.00[0.99–1.00];0.2454
SD of alkaline phosphatase	1.002[1.002–1.003];<0.0001***	1.002[1.001–1.003];0.0014**	1.003[1.002–1.003];<0.0001***	1.002[1.000–1.004];0.0359*
Alanine transaminase, U/L	1.000[1.000–1.001];0.3737	1.000[0.998–1.002];0.8684	0.999[0.995–1.002];0.3897	0.99[0.98–1.00];0.0914
SD of alanine transaminase	1.001[1.001–1.002];<0.0001***	1.001[1.000–1.002];0.0177*	1.001[1.000–1.003];0.0741	1.00[0.99–1.00];0.5347
Lipid, iron and calcium profile				
Total iron-binding capacity, L	1.00[0.98–1.02];0.9971	1.00[0.95–1.05];0.9678	0.99[0.95–1.04];0.7518	3.87[0.00–Inf];0.9993
VitaminB12, pmol/L	0.999[0.998–1.000];0.1739	1.00[0.99–1.00];0.1813	1.000[0.998–1.002];0.7853	1.00[0.99–1.01];0.8806
Folate, ng/mL	1.00[0.97–1.03];0.9877	1.04[0.97–1.12];0.2752	1.00[0.96–1.05];0.8835	1.04[0.95–1.14];0.3791
Ferritin, pmol/L	1.000[1.000–1.000];0.4438	1.000[1.000–1.000];0.3647	1.000[1.000–1.000];0.2525	1.000[1.000–1.001];0.1003
Calcium, mmol/L	0.64[0.39–1.06];0.0826	0.41[0.13–1.26];0.1212	0.91[0.36–2.28];0.8345	1.40[0.20–9.84];0.7350
SD of calcium	12.70[5.21–30.97];<0.0001***	2.10[0.13–34.34];0.6015	4.69[1.00–22.02];0.0499*	2.32[0.04–132.03];0.6840
Phosphate, mmol/L	0.83[0.59–1.18];0.3059	0.79[0.36–1.74];0.5548	0.98[0.50–1.90];0.9464	0.61[0.14–2.69];0.5115
SD of phosphate	5.97[3.23–11.04];<0.0001***	7.44[1.81–30.57];0.0054**	3.91[0.74–20.76];0.1098	18.22[0.41–815.46];0.1345
Inorganic, mmol/L	1.01[1.00–1.03];0.0836	0.99[0.94–1.04];0.7433	1.04[1.01–1.08];0.0055**	0.97[0.84–1.13];0.7058

* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors.

Characteristics	Before matching		After 1:2 matching	
	All-cause mortality	Composite outcome	All-cause mortality	Composite outcome
	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value	HR [95% CI];P value
SD of inorganic	1.00[0.95–1.07];0.8984	0.98[0.82–1.17];0.8125	1.08[0.85–1.36];0.5374	0.09[0.00-21.93];0.3871
Glycemic and clotting profile				
Triglyceride, mmol/L	0.96[0.88–1.05];0.3264	0.74[0.56–0.99];0.0436*	0.90[0.78–1.04];0.1556	0.61[0.35–1.09];0.0933
SD of triglyceride	0.84[0.64–1.11];0.2196	0.20[0.04–1.02];0.0526	0.69[0.41–1.17];0.1655	0.54[0.08–3.53];0.5213
Glucose, mmol/L	1.02[0.99–1.04];0.1738	1.00[0.94–1.05];0.9179	0.99[0.95–1.03];0.5861	0.90[0.79–1.04];0.1558
SD of glucose	1.06[1.02–1.11];0.0032**	1.07[0.98–1.16];0.1337	1.07[1.00-1.14];0.0580	1.07[0.92–1.23];0.3816
HbA1c, g/dL	0.97[0.95-1.00];0.0539	1.00[0.94–1.06];0.9969	0.95[0.91-1.00];0.0543	1.19[1.05–1.34];0.0072**
SD of HbA1c	1.58[1.44–1.74];<0.0001***	1.51[1.23–1.85];0.0001***	1.52[1.29–1.79];<0.0001***	1.94[1.36–2.76];0.0003***
High sensitive troponin-I, ng/L	1.000[1.000–1.000];0.9239	1.000[1.000–1.000];0.1181	1.000[1.000–1.000];0.9382	1.000[1.000–1.001];0.1785
SD of high sensitive troponin-I	1.000[1.000–1.000];0.7182	1.000[1.000–1.000];0.0044**	1.000[0.999–1.001];0.9978	1.000[1.000–1.001];0.2563
APTT, second	1.01[1.00-1.03];0.1426	0.98[0.93–1.03];0.3733	0.99[0.95–1.03];0.6325	0.98[0.89–1.08];0.6750
SD of APTT	1.05[1.02–1.08];0.0006***	0.99[0.90–1.10];0.8880	1.01[0.90–1.13];0.8927	1.10[0.86–1.42];0.4432
Lactate dehydrogenase, U/L	1.000[1.000–1.000];<0.0001***	1.000[1.000-1.001];0.0165*	1.000[1.000-1.001];0.0001***	1.000[0.999–1.001];0.6208
SD of lactate dehydrogenase	1.000[1.000–1.000];<0.0001***	1.000[1.000-1.001];0.0229*	1.002[1.001–1.002];<0.0001***	1.002[1.000-1.003];0.0056**
Total cholesterol, mmol/L	0.98[0.90–1.07];0.6769	0.92[0.75–1.13];0.4335	1.05[0.90–1.22];0.5598	1.42[1.00–2.00];0.0490*
SD of total cholesterol	1.14[0.84–1.55];0.3905	0.93[0.42–2.07];0.8677	1.23[0.73–2.07];0.4394	2.73[0.81–9.19];0.1058
Low-density lipoprotein, mmol/L	1.00[0.90–1.11];0.9905	0.96[0.76–1.22];0.7514	1.14[0.96–1.37];0.1398	1.67[1.14–2.45];0.0091**
SD of low-density lipoprotein	1.22[0.84–1.78];0.2952	1.13[0.45–2.83];0.7919	1.66[0.77–3.55];0.1928	7.64[1.84–31.77];0.0051**
High-density lipoprotein, mmol/L	0.93[0.73–1.19];0.5774	1.27[0.77–2.11];0.3530	0.97[0.62–1.50];0.8772	1.96[0.82–4.71];0.1309
SD of high-density lipoprotein	2.42[0.85–6.87];0.0971	1.55[0.11–21.84];0.7461	1.32[0.19–9.12];0.7758	1.09[0.01-164.28];0.9719
* for $p \leq 0.05$, ** for $p \leq 0.01$, *** for $p \leq 0.001$; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors.				

Sensitivity analysis

Supplementary Table 7 presented the adjusted hazard ratios (and 95% CIs) of PD-L1 v.s. PD-1 with cause-specific and subdistribution hazard competing risk analysis models for new onset cardiac composite and mortality outcomes after 1:2 propensity score matching. **Supplementary Table 8** presented the hazard ratios for associations of PD-L1 v.s. PD-1 using Cox proportional hazard model for adverse new onset cardiac composite and mortality outcome in the 1:2 matched cohort, with half-year lag time. **Supplementary Table 9** presented the risk of incident new onset cardiac composite and mortality outcomes associated with treatment of PD-L1 v.s. PD-1 with multiple matching adjustment approaches including propensity score stratification, high-dimensional propensity score matching, and propensity score matching with inverse probability of treatment weighting. The above analysis confirmed the protective effects of PD-L1 treatment over PD-1 treatment on new onset cardiac complications and mortality risks (HR < 1, P value < 0.05).

Prediction strength of subclinical inflammatory biomarkers

In the matched cohort, higher aspartate transaminase-to-alanine transaminase ratio (HR: 1.09, 95% CI: [1.04–1.14], P value = 0.0004) and higher monocyte-to-lymphocyte ratio (HR: 1.2, 95% CI: [1.02–1.43], P value = 0.0305) were significantly associated with all-cause mortality. A higher urea-to-creatinine ratio (HR: 1.01, 95% CI: [1.00-1.01], P value = 0.0007) was significantly associated with new onset cardiac composite outcome (Table 4). The boxplots of inflammatory biomarkers stratified by PD-1/PD-L1 inhibitor use and development of adverse outcomes are shown in Fig. 4.

Discussion

The main findings are that: i) the incidence of cardiovascular complications after PD-1 or PD-L1 inhibitor use was 16% in this territory-wide cohort of Chinese patients from Hong Kong, ii) multivariate Cox regression showed older age, a shorter average readmission interval and a higher number of hospital admissions were significant predictors of cardiovascular complications and iii) patients who developed cardiovascular complications had shorter average readmission interval and higher number of hospitalizations after treatment with PD-1/PD-L1 inhibitors.

Cardiac involvement in PD1 or PD-L1 inhibitors is variable, and can potentially affect the conduction system, myocardium or pericardium (16). Thus, heart block (17), Takotsubo cardiomyopathy (18), myocarditis (19, 20) and pericarditis (21) have been reported. A meta-analysis performed in 2018 found that anti-PD-1/PD-L1-related fatalities were often from pneumonitis (333 [35%]), hepatitis (115 [22%]), and neurotoxic effects (50 [15%]). Combination PD-1/ cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) deaths were frequently from colitis (32 [37%]) and myocarditis (22 [25%]) (22). In an analysis of the World Health Organization global database of adverse drug reactions in 2019, 2.1% of 106025 patients receiving PD-1 or PD-L1 inhibitors had cardiovascular complications (8). However, previous studies have largely been limited to case reports (17, 23), case series (24), single-center studies (25) or small registries (26, 27). In this territory-wide study from Hong Kong, we found that cardiovascular complications occurred in 16% of all patients receiving PD1 or PD-L1 inhibitors. Of these, the commonest is heart failure. Previously, acute heart failure has been described in the context of myocarditis (28), but heart failure without myocarditis has also been reported (29). Our study also identified cases of acute myocardial infarction following the initiation of PD-1/PD-L1 inhibitor therapy. Such findings would be in keeping with coronary toxicity that has been reported in the context of PD-1 inhibitor therapy (26).

Interestingly, our study did not identify any patients with myocarditis after treatment with PD-1 or PD-L1 inhibitors. Moreover, within the excluded patients with prior cardiovascular complications, none developed subsequent myocarditis. In 964 patients attending Massachusetts General Hospital, the incidence of myocarditis was 1.1% (n = 35) (27). In this cohort, myocarditis was more frequently observed in patients with pre-existing cardiovascular comorbidities. Nevertheless, another study using the VigiBase database found 101 cases of severe myocarditis, of which 75% of the myocarditis cases did not have pre-existing cardiovascular disease (30). A single-center study of 283 patients from China found only 3 cases (1.1%) of myocarditis, with variable presentations such as palpitations, dyspnea, and fatigue, or asymptomatic with incidental finding of grade 3 atrioventricular block and premature ventricular complexes on the electrocardiogram (25). In a pooled, retrospective review of three trials including 448 patients with advanced melanoma receiving PD-1/PD-L1 inhibitor therapy, no cases of myocarditis were identified (31). In association with myocarditis, different investigators have reported the presence of conduction abnormalities in the form of atrioventricular block (17, 24, 25, 32).

Limitations

There are some limitations of this study that should be acknowledged. Firstly, this was an administrative database study, and therefore cancer staging details could not be extracted. Secondly, under-coding or miscoding remains a possibility as with studies of a similar nature.

Conclusions

Compared with PD-1 inhibitor use, PD-L1 inhibitor use was significantly associated with lower risk of new onset composite outcome and all-cause mortality both before and after 1:1 propensity score matching. Patients who developed cardiovascular complications had shorter average readmission intervals and a higher number of hospitalizations after treatment with PD-1/PD-L1 inhibitors both before and after 1:1 propensity score matching.

Declarations

Consent for publication

N/A.

Availability of data and material

Data availability upon request to the corresponding author.

Competing interests

None.

Funding

None.

Authors' contributions

JZ, SL, GT: data analysis, data interpretation, statistical analysis, manuscript drafting, critical revision of manuscript

IL, SL, LY, TL, YX, YZ: data interpretation, manuscript drafting

EWC, ICKW: project planning, data acquisition, data interpretation, critical revision of manuscript

QZ: study conception, study supervision, project planning, data interpretation, statistical analysis, manuscript drafting, critical revision of manuscript

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Figures

Figure 1

IR: Incidence rate; PD-1: Programmed death 1 inhibitors; PD-L1: programmed death 1 ligand inhibitors. Study flow diagram describing derivation of the study cohort.

Figure 2

Kaplan-Meier survival curves of new onset cardiac complications and all-cause mortality in cancer patients stratified by PD-1 or PD-L1 inhibitor use before and after 1:2 propensity score matching.

Figure 3

Cumulative incidence curves of new onset cardiac complications and all-cause mortality in cancer patients stratified by PD-1 or PD-L1 inhibitor use before and after 1:2 propensity score matching.

Figure 4

Boxplots of subclinical inflammatory biomarkers stratified by PD-1/PD-L1 inhibitor use and adverse events development in the matched cohort.

Figure 5

Boxplots of significant laboratory examination variability to predict adverse outcomes stratified by PD-1/PD-L1 inhibitor treatment in the matched cohort.

Supplementary Files

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