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Clinical outcomes after immune checkpoint inhibitor-associated acute kidney injury: a cohort study

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ABSTRACT

Objectives Immune checkpoint inhibitors (ICPi) have significantly improved survival for patients with advanced cancers. However, the occurrence of ICPi-associated acute kidney injury (AKI) and its clinical impact remains unclear. This study evaluates the effects of ICPi-associated AKI (ICPi-AKI) on mortality, kidney and cardiovascular outcomes in patients undergoing ICPi treatments.

Design This multicentre retrospective cohort study with propensity score matching to balance baseline characteristics. The International Classification of Diseases, 10th Revision codes were used to identify individuals with cancer and treated with ICPi concurrently. Kaplan-Meier analyses coupled with log-rank tests were conducted to estimate the survival probabilities.

Setting Data were sourced from the TriNetX database spanning records from 25 March 2011 to 5 April 2024.

Participants Patients with cancer aged ≥18 years treated with ICPi with or without AKI occurrence.

Primary and secondary outcome measures The primary outcome was all-cause mortality, and secondary outcomes included major adverse kidney events (MAKE), major adverse cardiovascular events (MACE), the composite of MAKE or MACE with death, and end-stage renal disease.

Results The study identified 926 patients with cancer who developed ICPi-AKI (mean age, 67.1±11.8 years; 57.4% men). The control group consisted of 48 147 patients treated with ICPi but did not develop AKI (mean age, 65.3±13.1 years; 53.7% men). After matching, the ICPi-AKI group exhibited a higher risk of all-cause mortality (HR=1.27; 95% CI 1.02 to 1.61), MAKE (HR=3.83; 95% CI 1.72 to 8.40), MACE (HR=1.35; 95% CI 1.03 to 1.75)) compared with the non-ICPi-AKI group. Subgroup analyses confirmed these findings across various patient's characteristics.

Conclusion Individuals with ICPi-AKI are associated with an increased risk of all-cause mortality, MAKE and MACE. Enhancing awareness and timely intervention for ICPi-AKI are crucial for improving prognosis and reducing complications among patients with cancer.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We included all patients with cancer treated with immune checkpoint inhibitors (ICPi) and employed a propensity score matching approach to minimise potential confounding between the groups.
⇒ The study excluded patients with pre-existing end-stage renal disease, those on dialysis, and those using medications known to cause nephrotoxicity, ensuring that acute kidney injury (AKI) cases were newly developed post-ICPi administration.
⇒ The study relied on International Classification of Diseases, 10th revision diagnosis codes to identify ICPi-AKI cases, potentially introducing information bias due to variations in coding practices and diagnostic criteria.
⇒ The study lacked data on ICPi dosage, which may have influenced AKI risk and clinical outcomes, as some immune-related adverse events from ICPi are dose-dependent.

INTRODUCTION

Immune checkpoint inhibitors (ICPi) have revolutionised the treatment landscape of numerous advanced malignancies in the last decade.[1 2] To date, several ICPi have been approved by the US Food and Drug Administration (FDA) classified based on their targeted immune checkpoint molecules, including anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4) agents, anti-programmed cell death protein-1 (anti-PD-1) and anti-programmed cell death ligand-1 (anti-PDL1) agents.[2] These monoclonal antibodies target immune checkpoint molecules, enhancing T cell-mediated immune responses against tumour cells. This mechanism contributes to lasting anticancer responses and improved overall survival in patients with various cancers.[3] While ICPi reinvigorate the anti-tumor T-cell response, the increased immunological activation may lead to inflammatory side effects. These are known as immune-related adverse events (irAEs), affecting virtually any organ system.[3] Among the irAEs observed in patients receiving ICPi, skin-related irAEs are the most common reported (such as maculopapular rash and pruritus), followed by gastrointestinal toxicity, often presenting as diarrhoea or colitis and the third

most frequently reported are endocrine irAEs, including thyroid dysfunction and hypophysitis.[4] One notable but less commonly reported irAEs associated with ICPi is nephrotoxicity, which usually manifested as acute kidney injury (AKI), with an estimated incidence of 3%–5% from previous studies.[5] ICPi are now estimated to be indicated in approximately 36% of patients with advanced cancer.[6] Despite the increasing use of these immunotherapeutic agents, it remains unclear whether ICPi associated AKI (ICPi-AKI) impacts prognosis outcomes. Previous studies regarding the association between ICPi-AKI and subsequent mortality have shown inconclusive results. Meraz-Muñoz *et al*[7] reported that AKI was not associated with an increased risk of mortality, whereas García-Carro *et al*[8] concluded that AKI was an independent risk factor for mortality. To address this research gap, this study aims to explore the impact of ICPi associated with AKI on mortality, as well as kidney and cardiovascular outcomes among patients with cancer, based on real-world data.

METHODS

Data source

This retrospective-matched cohort study was conducted to evaluate the prognosis outcomes of ICPi-associated AKI in patients with cancer utilising data from the TriNetX Research Network, an international collaboration of health research platform.[9 10] This database gathers and aggregates real-time deidentified information from electronic health records, including demographics, diagnoses, procedures, laboratory data, medications and their types of healthcare organisations visits, thereby ensuring a comprehensive dataset spanning various geographic regions and healthcare settings.[10] This platform leverages interoperability and privacy-preserving integration of diverse electronic health record systems to enable data-driven study design.[9 10] Informed consent was not mandated because TriNetX contains anonymised data. The research was conducted in accordance with the Declaration of Helsinki and fully adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Study population

A search query identified a cohort of patients aged 18 years or older, diagnosed with cancer of all causes and received treatment with ICPi during the study period from 25 March 2011 to 5 April 2024. The start date was aligned with the approval of Ipilimumab, the first anti-CTLA-4 monoclonal antibody for use in patients with previously treated or newly diagnosed unresectable or metastatic melanoma, by the US FDA.[11] Patients diagnosed with cancer of all causes were identified using International Classification of Diseases, 10th revision codes (ICD10: C00-C96). Those who treated with ICPi were recruited based on the associated RxNORM and Healthcare Common Procedure Coding System codes. The study focused on a comprehensive array of approved ICPi, categorised by their mechanism of action, including anti-PD-1 antibodies (Nivolumab, Cemiplimab, Dostarlimab and Pembrolizumab), anti-PDL1 antibodies (Atezolizumab, Avelumab and Durvalumab) and anti-CTLA-4 antibody (Ipilimumab). The index date for analyses was defined as the first prescription of an approved ICPi subsequent to a diagnosis of cancer in both groups. Individuals with pre-existing end-stage renal disease (ESRD) or were dependent on dialysis on or before the index date were excluded to prevent misidentifying incident adverse kidney outcomes. According to Cortazar *et al*[12] and Gupta S *et al*,[5] ICPi-AKI typically occurred at a median of 16 weeks following the initiation of ICPi therapy, and at a median of 2 weeks after the administration of the last dose of ICPi. Therefore, we established the observation window of ICPi-AKI between 1 and 16 weeks post-ICPi initiation. Previous studies[7 12 13] have identified certain medications as potential contributors to AKI associated with ICPi, including the concurrent use of proton pump inhibitors (PPI),[14] non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARB), diuretics and cisplatin. To minimise confounding factors, individuals who used any of these medications within one to 16 weeks after the index prescription of ICPi were excluded. The study cohort was subsequently divided into two groups: those who developed AKI within 1 to 16 weeks after ICPi initiation (ICPi-AKI group) and those who did not experience AKI episode during the same timeframe following the start of ICPi therapy (non-ICPi AKI group). In addition, for ICPi-AKI patients, we categorised them into two groups: those with renal recovery and those without. Recovery from ICPi-AKI was defined as the absence of any diagnosis of AKI, chronic kidney disease (CKD) or proteinuria within 90 days after the AKI episode. Conversely, lack of recovery from ICPi-AKI was defined as having a diagnosis of AKI, CKD or proteinuria within the same 90-day period following the AKI event. This classification ensured a clear distinction between patients who recovered renal function and those who progressed to chronic or unresolved kidney conditions after the initial AKI episode.

Details of the codes used to define the cohorts are provided in online supplemental table 1.

Covariates

In the current study, the following variables were considered for propensity score matching (PSM) to adjust for differences in baseline characteristics between two groups: demographic characteristics (age, gender, race and ethnicity), baseline comorbidities (dyslipidaemia, hypertension (HTN), cerebrovascular diseases, CKD], malignant neoplasms (digestive organs, skin, bronchial and lung, urinary tract and ill-defined or secondary cancers), the presence of ICD-10 codes for regional or distant metastases (secondary malignant neoplasm of lymph nodes, respiratory and digestive organs, other, unspecified sites and secondary neuroendocrine tumours). Additionally,

adjustments were made for systolic and diastolic blood pressure, obesity (body mass index (BMI) ≥30 kg/m^2), glycated haemoglobin (HbA1c, ≥7%), estimated glomerular filtration rate (eGFR), albumin (<30 g/dL). Detailed information about the covariates, including their codes, is listed in online supplemental table 2.

Study outcomes

The primary outcome was all-cause mortality, and the secondary outcomes included the incidence of major adverse kidney events (MAKE), major adverse cardiovascular events (MACE), the composite of MAKE or all-cause mortality, the composite of MACE or all-cause mortality and ESRD. MAKE encompassed stage 5 CKD, ESRD, dependent on dialysis dependence and kidney transplantation, while MACE was specifically defined as myocardial infarction, ischaemic stroke, haemorrhagic stroke, heart failure, ventricular arrhythmia and sudden cardiac death. ESRD comprised end-stage kidney disease, need for dialysis therapy or kidney transplantation. These outcomes were observed within a period ranging from 16 weeks to 1 year after the index date. Sensitivity analyses were conducted comparing the primary and secondary outcomes between the ICPi-AKI and non-ICPi-AKI groups, using different cut-off landmarks (16 weeks to 6 and 8 months after the index date). Besides, negative control outcomes including age-related cataract, sensorineural hearing loss and otitis media were applied to support the validity of the study results. In patients who experienced ICPi-AKI, a comparative analysis was conducted to evaluate the prognostic outcomes between those who recovered renal function within 3 months post-AKI period and those who progressed to CKD. Additional details regarding the variables and their corresponding ICD-10 codes are provided in online supplemental table 3.

Statistical analysis

All statistical analyses were conducted using the built-in functions from the TriNetX platform. Baseline characteristics of the two groups are presented as mean±SD, or as counts and percentages, depending on the nature of the covariates. To reduce the likelihood of confounders, one-to-one PSM was performed based on the greedy nearest-neighbour algorithm with a calliper of 0.1 pooled standardised differences. TriNetX randomised the order of rows in order to eliminate bias resulting from nearest neighbour algorithms. Postmatching variables with standardised differences below 0.1 between groups were deemed to be adequately matched. After matching, Kaplan-Meier analyses coupled with log-rank tests were conducted to estimate the survival probabilities. Results of each outcome were expressed as HRs with corresponding 95% CIs. Two-sided p value of <0.05 was considered statistically significant. Outcome variables were classified as either present or absent, rendering missingness irrelevant. To reduce errors caused by incomplete data, cases that were not followed up after the index visit were excluded. Furthermore, the effect of ICPi-AKI on the risk of mortality, MAKE, MACE was evaluated within prespecified subgroups by age (<65 or ≥65 years), sex (male or female), years of ICPi approval (2011–2017 or 2018–2024), prior nephrotoxicity chemotherapy before the index date, cancer type (urinary tract, digestive organs, melanoma or skin related, or bronchus and lung, baseline autoimmune disease, different treatment strategy of ICPi (anti-PD-1, anti-PDL1, anti-CTLA 4 or anti-PD-1+ anti-CTLA 4), CKD stage (stage 1–2 or 3–4), baseline HTN and type 2 diabetes mellitus (DM). P value for interaction was also performed to assess whether the effect of the aforementioned variables was consistent across different subgroups. A statistically significant interaction was indicated at p value <0.05. To ensure patient anonymity, outcomes involving fewer than 10 patients are rounded up to 10 in all reported calculations.

RESULTS

Baseline characteristics

After excluding ineligible participants, 49 073 patients diagnosed with cancer and treated with ICPi were identified in the study period. Among them, 926 experienced AKI after ICPi initiation, while 48 147 without AKI episode after ICPi therapy, as shown in figure 1. Prior to matching, the mean age at index of patients with ICPi-AKI was 67.1 years, compared with 65.3 years for the non-ICPi AKI group. Regarding the ethnicity distribution, the ICPi-AKI group had a lower proportion of individuals identifying as white (70% vs 72.7%), Hispanic or Latino (3.6% vs 3.9%), unknown race and ethnicity (24.4% vs 28.4%) and higher proportion of individuals who were Asian (3.3% vs 3.1%) or African American (11.2% vs 7.0%). Furthermore, variations were observed in the distribution of comorbidities between the two groups. The prevalence of dyslipidaemia, HTN, cerebrovascular disease, CKD stage 3 or 4 was higher in the ICPi-AKI group. In terms of secondary malignancy, before matching, the ICPi-AKI cohort exhibited a higher percentage of having metastatic disease, which was classified using ICD-10 codes covering the site of lymph nodes, respiratory and digestive organs, neuroendocrine tumour or others. In addition, compared with the ICPi AKI group, fewer individuals in the non-ICPi-AKI group had an eGFR of 30–59 or 15–29 mL/min/1.73 m^2, HbA1c ≥7%, Albumin <30 g/L or BMI ≥30 kg/m^2. The proportion of corticosteroid use in the ICPi-AKI group was lower compared with the non-ICPi-AKI group. Following PSM, 910 patients were identified in each group with well-balanced baseline characteristics, with standardised mean differences for all variables being <0.1 (table 1).

Primary and secondary outcome

Among patients with cancer and treated with ICPi, 140 of 910 patients (15.4%) in the ICPi-AKI group and 132 of 910 patients (14.5%) in the non-ICPi-AKI group experienced all-cause mortality during the follow-up period. The ICPi-AKI group exhibited a significantly higher risk

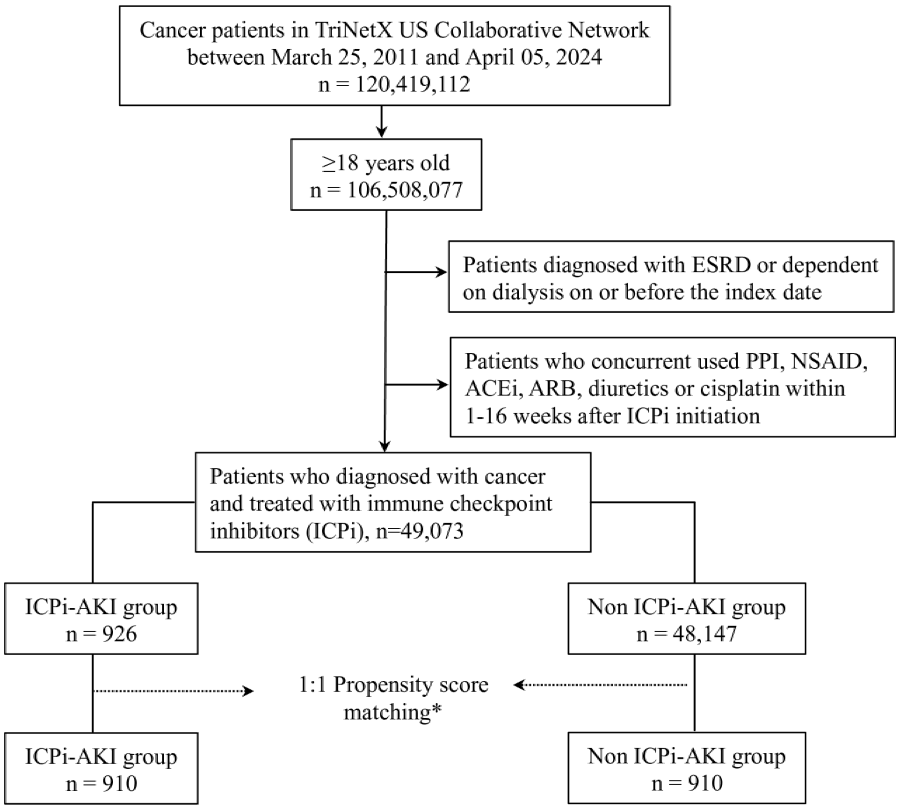

Figure 1 Flowchart of cohort construction. *1:1 Propensity score matching, by demographics, comorbidities, BMI, laboratory test results and presence of regional or distant metastases. ACEi, ACE inhibitors; AKI, acute kidney injury; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; ESRD, end-stage renal disease; ICPi, immune checkpoint inhibitor; NSAID, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor.

of all-cause mortality (HR=1.27; 95% CI 1.02 to 1.61; log-rank test, p=0.048) compared with the non-ICPi-AKI group (figure 2). 26 of 910 patients (2.9%) in the ICPi-AKI group and 10 of 910 patients (1.1%) in the non-ICPi-AKI group had MAKE. The hazard of MAKE was significantly higher in the ICPi-AKI group to the non-ICPi-AKI group (HR=3.83; 95% CI 1.72 to 8.40; log-rank test, p<0.001). A similar trend was observed in the outcome of MACE. There were 118 out of 910 patients (13.0%) in the ICPi-AKI group and 105 out of 910 patients (11.5%) in the non-ICPi-AKI group had MACE. Patient who experienced AKI following ICPi therapy had higher risk of developing MACE (HR=1.35; 95% CI 1.03 to 1.75; log-rank test, p=0.027) compared with those without. The risk for MAKE or all-cause mortality (HR=1.39; 95% CI 1.10 to 1.74; log-rank test, p=0.005), MACE or all-cause mortality (HR=1.33; 95% CI 1.10 to 1.61; log-rank test, p=0.003) were also higher in ICPi-AKI group compared with the non-ICPi-AKI group (table 2 and figure 2). However, there was no significant difference between the two groups in terms of the risk of ERSD (HR=1.98; 95% CI 0.47 to 8.28; log-rank test, p=0.34).

Subgroup analyses and sensitivity analyses

Compared with the non-ICPi-AKI group, the ICPi-AKI group had significantly and consistently higher HR for the all-cause mortality among most subgroups, including patients aged <65 (HR=1.70; 95% CI 1.02 to 2.84), men (HR=1.47; 95% CI 1.06 to 2.04), women (HR=1.60; 95% CI 1.05 to 2.45), years of ICPi approval from 2018 to 2024 (HR=1.43; 95% CI 1.10 to 1.86), urinary tract cancer (HR=1.97; 95% CI 1.07 to 3.65), and those without baseline autoimmune disease (HR=1.41; 95% CI 1.09 to 1.84). No statistically significant interactions were observed between the subgroup variables, as all p values for interaction being greater than 0.05. However, p value for interaction regarding anti-CTLA4 was not estimable as there were no incidences of mortality in the non-ICPi-AKI cohort (figure 3).

In terms of secondary outcomes, the significant higher risk of MAKEs was consistently observed in the following estimated subgroups, including patients aged <65 years (HR=3.82; 95% CI 1.03 to 14.13) or ≥65 years (HR=2.98; 95% CI 1.25 to 7.15), years of ICPi approval during 2018 to 2024 (HR=2.73; 95% CI 1.35 to 5.53), patients who received nephrotoxicity chemotherapy before ICPi initiation (HR=5.88; 95% CI 1.29 to 26.84), those who did not received nephrotoxicity chemotherapy before ICPi initiation (HR=2.41; 95% CI 1.04 to 5.59), those without baseline autoimmune disease (HR=3.19; 95% CI 1.48 to 6.87), those who received anti-PD-1 therapy (HR=3.35; 95% CI 1.32 to 8.49) and patients who did not have history of HTN (HR=3.69; 95% CI 1.20 to 11.32) or DM (HR=4.49; 95% CI 1.68 to 12.02). No statistically significant interactions were found in the investigated

Table 1 Baseline characteristics of patients before and after propensity score matching

Characteristics	Patient groups					
	Before matching			After matching		
	ICPi-AKI (n=926)	ICPi without AKI (n=48 147)	Std. diff.	ICPi-AKI (n=910)	ICPi without AKI (n=910)	Std. diff.
Demographics						
Age at index (mean±SD, year)	67.1±11.8	65.3±13.1	0.146	67.1±11.8	67.5±11.9	0.039
Sex, n (%)						
Male	522 (57.4)	26 603 (53.7)	0.073	522 (57.4)	535 (58.8)	0.029
Female	320 (35.2)	19 995 (40.4)	0.108	320 (35.2)	309 (34.0)	0.025
Race and ethnicity, n (%)						
White	637 (70.0)	35 998 (72.7)	0.061	637 (70.0)	663 (72.9)	0.063
Asian	30 (3.3)	1558 (3.1)	0.009	30 (3.3)	29 (3.2)	0.006
Black or African American	102 (11.2)	3449 (7.0)	0.148	102 (11.2)	87 (9.6)	0.054
Hispanic or Latino	33 (3.6)	1923 (3.9)	0.014	33 (3.6)	25 (2.7)	0.050
Unknown race	112 (12.3)	6502 (13.1)	0.025	112 (12.3)	110 (12.1)	0.007
Unknown ethnicity	222 (24.4)	14 059 (28.4)	0.091	222 (24.4)	224 (24.6)	0.005
Comorbidities, n (%)						
Dyslipidaemia	363 (39.9)	17 299 (34.9)	0.102	363 (39.9)	389 (42.7)	0.058
Hypertension	460 (50.5)	21 260 (42.9)	0.153	460 (50.5)	471 (51.8)	0.024
Cerebrovascular disease	95 (10.4)	4847 (9.8)	0.022	95 (10.4)	85 (9.3)	0.037
CKD, stage 3	81 (8.9)	3076 (6.2)	0.102	81 (8.9)	81 (8.9)	<0.001
CKD, stage 4	14 (1.54)	403 (0.8)	0.067	14 (1.54)	10 (1.1)	0.039
Secondary malignancy, n (%)						
Lymph nodes	295 (32.4)	15 522 (31.4)	0.023	295 (32.4)	296 (32.5)	0.002
Respiratory and digestive organs	309 (34.0)	13 345 (27.0)	0.153	309 (34.0)	303 (33.3)	0.014
Neuroendocrine tumour	15 (1.6)	631 (1.3)	0.031	15 (1.6)	13 (1.4)	0.018
Other	431 (47.4)	18 838 (38.1)	0.189	431 (47.4)	429 (47.1)	0.004
Malignant neoplasms, n (%)						
Respiratory organs	308 (33.9)	18 104 (36.6)	0.057	308 (33.9)	350 (38.5)	0.096
Digestive organs	151 (16.6)	7232 (14.6)	0.055	151 (16.6)	138 (15.2)	0.039
Melanoma or skin related	173 (19.0)	11 404 (23.0)	0.099	173 (19.0)	205 (22.5)	0.087
Kidney, except renal pelvis	137 (13.9)	4529 (8.8)	0.163	137 (13.9)	138 (14.0)	0.003
Renal pelvis	19 (1.9)	659 (1.3)	0.052	19 (1.9)	16 (1.6)	0.023
Ureter	15 (1.5)	543 (1.0)	0.042	15 (1.5)	15 (1.5)	<0.0001
Bladder	123 (12.5)	3577 (6.9)	0.189	123 (12.5)	98 (9.9)	0.081
Other and unspecified urinary organs	56 (5.7)	1640 (3.17)	0.123	56 (5.7)	63 (6.4)	0.030
Laboratory tests						
Blood pressure, systolic (mean±SD, mm Hg)	130±21.7	127±20	0.132	130±21.7	128±19.8	0.091
Blood pressure, diastolic (mean±SD, mm Hg)	73.5±11.2	72.9±11.6	0.048	73.5±11.2	72.8±11.3	0.057
Glycated haemoglobin≥7%	58 (6.4)	3129 (6.3)	0.002	58 (6.4)	71 (7.8)	0.056
eGFR: 30–59 (mL/min/1.73 m^2)	451 (49.6)	16 498 (33.3)	0.334	451 (49.6)	467 (51.3)	0.035
eGFR: 15–29 (mL/min/1.73 m^2)	61 (6.7)	2462 (5.0)	0.074	61 (6.7)	53 (5.8)	0.036
Albumin<30 g/L	760 (83.5)	39 820 (80.4)	0.080	760 (83.5)	782 (85.9)	0.067
BMI≥30 kg/m^2	149 (16.4)	6754 (13.6)	0.076	149 (16.4)	150 (16.5)	0.003
Medications						
Corticosteroids	625 (61.3)	35 695 (64.2)	0.060	625 (61.3)	613 (60.1)	0.024

AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICPi, immune checkpoint inhibitor; Std. diff, standard difference.

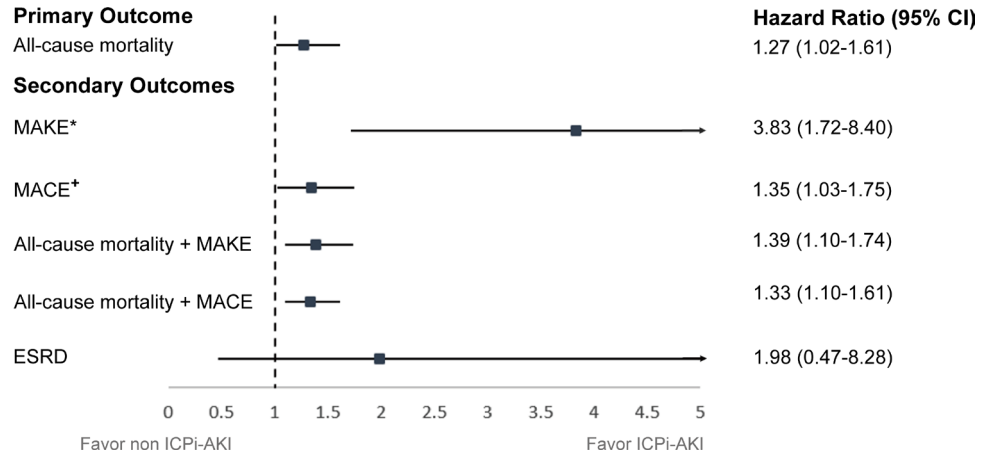

Figure 2 Forest plot of primary and secondary outcomes. *MAKE: defined as stage 5 CKD, end-stage kidney disease, dependent on dialysis and kidney transplantation.+MACE: defined as myocardial infarction, ischaemic stroke, haemorrhagic stroke, heart failure, ventricular arrhythmia, and sudden cardiac death. AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; ICPi, immune checkpoint inhibitor; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events.

subgroups, with all interaction p values greater than 0.05 (online supplemental figure 1). Moreover, the higher risk of the MACEs among ICPi-AKI group than non-ICPi-AKI group was observed across some subgroup, including patients aged under 65 (HR=2.20; 95% CI 1.16 to 4.17), those with melanoma or skin-related cancer (HR=2.12; 95% CI 1.03 to 4.38), those who did not have baseline autoimmune disease (HR=1.41; 95% CI 1.06 to 1.86), patients who received anti-PD-1 and anti-CTLA4 concurrently as ICPi therapy (HR=2.16; 95% CI 1.04 to 4.49) and those who did not have history of DM (HR=1.41; 95% CI 1.01 to 1.96) (online supplemental figure 2). Concerning the composite outcome of death and MAKE, the findings were also consistent across the investigated subgroups (online supplemental figure 3). Finally, in the context of the composite outcome of all-cause mortality or MACE, the ICPi-AKI group exhibited a higher risk compared with the non-ICPi-AKI group in all subgroups. (online supplemental figure 4).

Regarding sensitivity analyses, we employed different cut-off points at 6 and 8 months postindex date for the initiation of follow-up, demonstrating consistent results across all primary and secondary outcomes when compared with our main analysis (online supplemental table 4). Patients who developed AKI after treating with ICPi had higher risk of all-cause mortality (HR=1.79; 95% CI 1.23 to 2.60; log-rank test, p=0.002), MAKE (HR=7.34; 95% CI 2.18 to 24.71; log-rank test, p<0.001), MACE (HR=1.85; 95% CI 1.31 to 2.62; log-rank test, p<0.001), all-cause mortality or MAKE (HR=2.02; 95% CI 1.42 to 2.88; log-rank test, p<0.001) and all-cause mortality or MACE (HR=1.85; 95% CI 1.41 to 2.42; log-rank test, p<0.001) in 6 months after ICPi initiation. Similarly, the ICPi-AKI group showed higher risks of all-cause mortality (HR=1.49; 95% CI 1.12 to 1.97; log-rank test, p=0.006), MAKE (HR=2.76; 95% CI 1.27 to 5.99; log-rank test, p=0.008), MACE (HR=1.56; 95% CI 1.16 to 2.10; log-rank test, p=0.003), all-cause mortality or MAKE (HR=1.54;

Table 2 HR of primary and secondary outcomes for the matched groups

Outcome	Number of patients with outcome		HR (95% CI)	P value
	ICPi with AKI (n=910)	ICPi without AKI (n=910)		
Primary outcome				
All-cause mortality	140	132	1.27 (1.02 to 1.61)	0.048
Secondary outcome				
MAKE	26	10	3.83 (1.72 to 8.40)	<0.001
MACE	118	105	1.35 (1.03 to 1.75)	0.027
All-cause mortality+MAKE	158	138	1.39 (1.10 to 1.74)	0.005
All-cause mortality+MACE	226	207	1.33 (1.10 to 1.61)	0.003
ESRD	10	10	1.98 (0.47 to 8.28)	0.34

AKI, acute kidney injury; ESRD, end-stage renal disease; ICPi, immune checkpoint inhibitor; MACE, major adverse cardiovascular events; MAKE, major adverse kidney events.

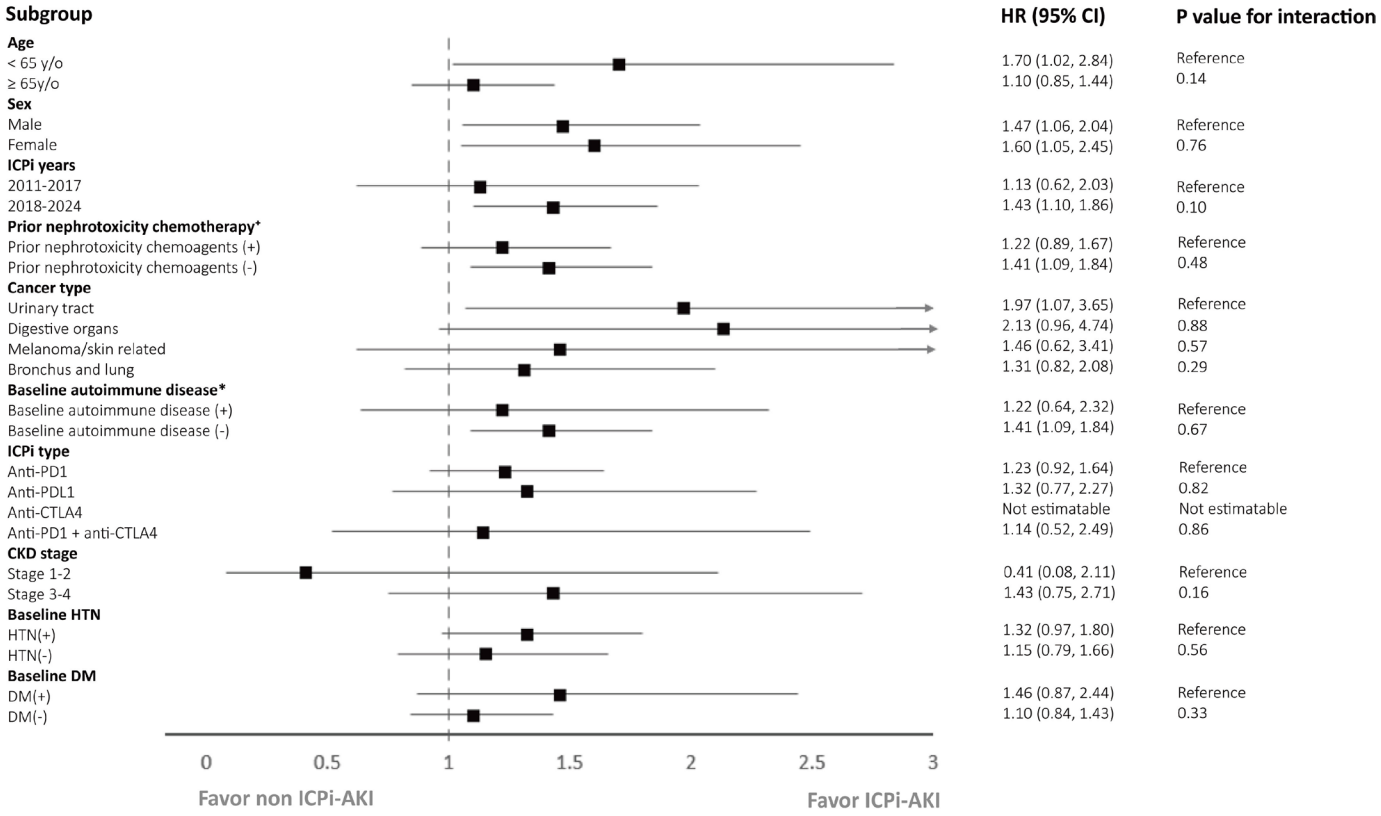

Figure 3 Subgroup analyses of the primary outcome (all-cause mortality) in patients who developed AKI under ICPi treatment compared with those without. [+]Prior nephrotoxicity chemotherapy: defined as using chemotherapy drugs which were prescribed before ICPi initiation, such as cisplatin, carboplatin, oxaliplatin, gemcitabine, capecitabine, cyclophosphamide, methotrexate, topotecan, irinotecan, vemurafenib, bortezomib. AKI, acute kidney injury; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HTN, hypertension; ICPi, immune checkpoint inhibitor; y/o, year old.

95% CI 1.18 to 2.01; log-rank test, p=0.001) and all-cause mortality or MACE (HR=1.58; 95% CI 1.27 to 1.97; log-rank test, p<0.001) 8 months following the initiation of ICPi therapy. The risk of developing ESRD was similar between the two groups, irrespective of the follow-up period being 6 or 8 months postintervention. As for the negative control outcomes, no significant differences were found with all negative control outcomes between two groups (online supplemental table 5). Finally, ICPi-AKI patients who did not achieve complete renal recovery demonstrated poorer outcomes compared with those who did. The risks of MAKE (HR=1.79, 95% CI 1.37 to 2.36, p<0.001), MACE (HR=3.34, 95% CI 1.42 to 7.84, p=0.003), the composite outcome of all-cause mortality or MAKE (HR=1.78, 95% CI 1.37 to 2.31, p<0.001) and the composite outcome of all-cause mortality or MACE (HR=1.92, 95% CI 1.13 to 2.36, p<0.001) were markedly higher in the non-recovery group. However, there was no statistically significant difference on all-cause mortality between two groups (HR=1.36, 95% CI 0.69 to 2.68, p=0.37) (online supplemental table 6).

DISCUSSION

This cohort study of 49 073 individuals with cancer and developing AKI following any of ICPi therapy showed a significantly higher risk of all-cause mortality, MAKE, MACE, the composite of MAKE or all-cause mortality and the composite of MACE or all-cause mortality, when compared with the non-ICPi-AKI group. In addition, the higher risk of all-cause mortality, MAKE, MACE and the composite of MAKE or all-cause mortality remained consistent in the subgroup analyses by age, sex, ICPi approval years, history of prior nephrotoxicity chemotherapy, cancer types, history of autoimmune disease, different classes of ICPi, stages of CKD, and history of HTN or DM. Altogether, these findings reinforced the notion that patients with cancer with ICPi-AKI have increased susceptibility to worse prognostic outcomes.

Regarding all-cause mortality, a meta-analysis[15] revealed that patients who developed AKI during ICPi therapies had 51% increased risk of death compared with those without; the findings are generally in accordance with our study. According to the American Society of Clinical Oncology guideline,[16] the guideline suggested that the cessation of the culprit drug is the first step in the management of patients with ICPi-AKI. Given the established efficacy of ICPi in altering cancer progression and improving survival rates by the abrogation of immune-checkpoint signalling, it stands to reason that discontinuing ICPi therapy may lead to tumour progression and, consequently, higher mortality rates. Moreover, previous studies[12 17] had highlighted that the absence of kidney

recovery in patients with ICPi-AKI was independently associated with reduced survival. Our study demonstrated a higher likelihood of subsequent MAKE in patients who experienced AKI following ICPi administration. It is speculated that the lower proportion of kidney recovery within our cohort contributes to the observed higher mortality rates. In addition, ICPi enhance anti-tumour response by blocking T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), a receptor that suppresses immune responses, thereby augmenting the activity of cytotoxic T cells and NK cells while concurrently reducing the inhibitory function of regulatory T cells.[18] Recent study[19] implicated that TIGIT may mediate kidney T cell contributions to AKI. TIGIT expression is markedly upregulated on kidney T cells during AKI, facilitating the production of proinflammatory cytokines and the persistence of effector and central memory T cell phenotypes. The augmentation of inflammatory response can potentiate kidney injury, as evidenced by experimental models of ischaemic and nephrotoxic AKI where TIGIT-deficient mice exhibit less kidney damage and improved outcomes.[19] ICPi-AKI can result in irreversible organ damage even after immunosuppressive therapy has successfully halted immunologic activity.[12] This phenomenon may be partly due to the insidious progression of acute tubulointerstitial nephritis (ATIN), the most common injury pattern of ICPi-AKI, and the limited sensitivity of serum creatinine as a marker of early detection of renal injury.[12] These factors collectively enable ATIN to persist undetected for prolong periods, only being identified once significant and irreversible kidney damage has occurred, potentially explaining the increased risk in MAKE outcomes in our study.

The overall MACE risk is significantly higher in patients who developed AKI after ICPi treatments. Emerging evidence indicates that ICPi treatment is associated with cardiovascular toxicity, manifesting as autoimmune T-cell-mediated myocarditis, arrhythmia, venous thromboembolic disease, accelerated atherosclerosis and atherosclerosis-related cardiovascular events.[20 21] The association between ICPi and the rising incidence of cardiovascular events extends beyond the initial weeks of treatments, with such events potentially occurring months to years after ICPi therapy.[21] Furthermore, as the survival of patients with ICPi therapy continues to improve, the potential for cardiac injury and dysfunction may be amplified, leading to de novo cardiac events such as acute myocardial infarction. In a real-world analysis[22] demonstrated that the risk of ICPi-associated cardiovascular adverse events, including acute myocardial infarction, stroke, conduction disorders and heart failure were higher in patients undergoing ICPi therapy. Additionally, kidney irAEs have been significantly associated with the development of cardiotoxicity, which may be attributed to off-target immune effects in the heart from immune system overactivation.[22] These findings provide a comprehensive explanation for our study results.

Strengths and limitations

There are some strengths in our research. First, we included all patients with cancer treated with ICPi and employed a PSM approach to minimise potential confounding between the groups. Second, this is the first real-world study focused on the prognosis outcomes in patients who developed AKI following ICPi treatments. The findings were consistent across almost all subgroup analyses. Moreover, determining whether ICPi-AKI is exclusively related to ICPi can be challenging. To address this, we excluded patients with pre-existing ESRD or those dependent on dialysis prior to the initiation of ICPi initiation. We also excluded individuals who were concurrently using medications known to cause nephrotoxicity, such as PPIs, NSAIDs and ARBs. These measures ensured that the observed AKI was newly developed following ICPi administration. Therefore, this study provides updated information with robust evidence and high generalisability. These findings contribute significantly to our understanding of ICPi-associated kidney and prognostic outcomes in a diverse, real-world patient population.

Nevertheless, there were some limitations in our study. First, we used ICD-10 diagnosis codes to identify cases of ICPi-AKI rather than the standard definition, which requires a 1.5-fold or greater increase in serum creatinine levels within a 7-day period. This approach may introduce information bias due to difference in coding practices and diagnostic criteria. Second, residual confounding could not be completely avoided because the database we used is subjected to inherent to an electronic health records study, though we applied PSM and negative control outcomes suggested that biases from these factors were likely not significant. Finally, our study lacked information about the dosage of ICPi due to the limitation of TriNetX database, which may have influenced the observed AKI risk and further affected clinical outcomes in cancer populations. A previous study reported that irAEs from certain ICPi are dose-dependent.[23]Further investigations into the potential relationship between ICPi dose and kidney-related irAE are needed.

CONCLUSION

In conclusion, the development of AKI in patients with cancer receiving ICPi significantly increased the risk of all-cause mortality, MAKE and MACE compared with those without ICPi-AKI. Given the increasing number of patients with cancer treated with ICPi, although kidney complications such as AKI from ICPi are infrequent, it is crucial to prioritise the early detection and timely intervention of kidney-related irAEs to reduce adverse health outcomes.

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