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Concomitant Proton Pump Inhibitors and Immune Checkpoint Inhibitors Increase Nephritis Frequency

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Abstract. *Background/Aim: Concomitant proton pump inhibitor (PPI) and immune checkpoint inhibitor (ICPI) were determined as risk factors of acute kidney injury. To identify the type of PPI associated with ICPI-induced nephritis, we used the Japanese Adverse Drug Event Report database. Patients and Methods: ICPIs (nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, and avelumab) and PPIs (esomeprazole, omeprazole, vonoprazan, rabeprazole, and lansoprazole) were selected as suspected nephritis-inducing drugs. Results: The cases of concomitant use of atezolizumab and rabeprazole, ipilimumab and omeprazole, ipilimumab and lansoprazole, nivolumab and esomeprazole, nivolumab and omeprazole, nivolumab and rabeprazole, nivolumab and lansoprazole, pembrolizumab and esomeprazole, as well as pembrolizumab and lansoprazole had a significantly higher reported odds ratio than monotherapy cases. Conclusion: Male patients or patients using ICPIs and PPIs (excluded vonoprazan) concomitantly should be monitored for renal function after chemotherapy.*

Immune checkpoint inhibitors (ICPIs) are used as essential anti-cancer chemotherapy in various types of cancers (1-5). Blockade of programmed cell death-1 (PD-1)/PD-ligand-1 signaling (6, 7) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) signaling (8) activates T-cell mediated antitumor immunity; therefore, ICPIs exert dramatic effects in patients with cancer expressing these proteins. As ICPIs induce antitumor effects by reactivating antitumor immunity, they also cause immune-related adverse events (irAEs), such as interstitial pneumonia and nephritis (9-11), thyroid dysfunction (5, 9), type 1 diabetes mellitus (5), and lupus erythematosus (12). The clinical features and outcomes of ICPI-induced acute kidney injury (AKI) have been reported (13-15). As a pathological feature, acute tubulointerstitial nephritis was the primary pathologic lesion with lymphocyte infiltration. In addition, lower baseline estimated glomerular filtration rate (eGFR), use of proton pump inhibitor (PPI), and ICPI combination were determined as risk factors of ICPI-associated AKI (13). Furthermore, the mortality of patients with renal recovery after ICPI-induced nephritis was better than that of patients without renal recovery (16). To improve prognosis for patients treated with ICPIs, the prevention of ICPI-induced nephritis is essential.

PPIs are traditionally widely used for the treatment of several acid-related disorders, including peptic ulcer disease, gastroesophageal reflux disease, and *Helicobacter pylori* eradication. Although the use of PPIs was perceived as safe, it is associated with the incidence of AKI (17-22). In particular, omeprazole is associated with acute interstitial nephritis (AIN) (17). Because AKI and AIN increase the risk of chronic kidney disease (CKD), the prevention of PPI-induced AIN could decrease the initiation of dialysis (23-25).

Since the frequency of overall incidence of ICPI-induced AKI is 2.2% (26), the information regarding ICPI-induced AKI is limited. In addition, it remains unclear as to which PPIs increase the risk of AKI. The Japanese Adverse Drug Event Report (JADER) database is an open-access database of adverse drug events (ADEs). The JADER database is useful for calculating ADE signals in rare cases. The frequencies of irAEs associated with ICPIs were approximately 50% (skin disorders), 40% (gastrointestinal disorders), 8% (endocrine disorders), 4% (hepatitis), and 1% (pneumonitis) in advanced melanoma (14). Because of

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their low frequency, the signals of irAEs for nephritis/renal dysfunction, pneumonitis, rash, and type 1 diabetes mellitus associated with ICPIs were calculated using JADER (27). However, information on drug-drug interactions is limited. In this study, we aimed to elucidate the type of PPI associated with ICPI-induced nephritis and used the JADER database.

Patients and Methods

Data source. Data from April 2004 to September 2020 were extracted from the JADER database. The JADER database consists of four data tables: patient demographic information (demo), drug information (drug), ADEs (reac), and primary disease (hist). The duplicated data in the "drug" and "reac" tables were removed, and the "demo" table was linked to the "drug" and "reac" tables using each case identified in the data tables. In these cases, the contribution of the medications to the ADEs was classified into three categories: "suspected medicine", "concomitant medicine", and "interaction". The "suspected medicine" category was extracted into ADEs in the present study.

The "demo" table contained data for patient sex and age, as well as other patient characteristics. Data without sex or age information were excluded from the dataset. For the association analysis performed with patients classified in 10-year age intervals, we defined "older adults" as those in their "70s", "80s", "90s", and "100s", according to a previous report (28). Nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, and avelumab were selected as suspected drugs for analysis of irAEs. These ICPIs have been approved by the Japanese Ministry of Health, Labor, and Welfare.

Definition of cancer patients. The primary disease in the "hist" tables was defined on the basis of the preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. MedDRA term grouping at the PT level defines the patient's medical condition. Cancer as a primary disease as defined by PTs is shown in Table I after removing duplicated data. Other cancers not included in Table I that appeared as primary diseases were classified as others/uncertain.

Definition of ICPIs and nephritis as irAEs. ICPIs (nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, and avelumab) and PPIs (esomeprazole, omeprazole, vonoprazan, rabeprazole, and lansoprazole) were selected as suspected nephritis-inducing drugs. The ADEs in the "reac" table were coded according to the PTs in the MedDRA. Nephritis as an irAE was selected by three nephrologists from the MedDRA, and the PTs for nephritis are listed in Table II.

Statistical analysis. The reporting odds ratio (ROR), which serves as an index for adverse event signals, was calculated using the following equations (28), with a, b, c, and d cross-tabulation as follows: a, number of cases with an ADE related to the use of the suspected drug; b, number of cases with an ADE related to the use of all other drugs; c, number of cases with all other ADEs related to the use of the suspected drug; and d, number of cases with all other ADEs related to the use of all other drugs.

$$ROR=(a/b)/(c/d)=ad/bc$$

Adverse event signals were recognized as significant when the ROR estimates and the lower limits of the corresponding 95% confidence interval (CI) exceeded 1. RORs were calculated using Excel for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA). The signals of drug-drug interactions were evaluated as significant when the lower limits of the corresponding 95% CI in drug-drug interactions exceeded the higher limits of the corresponding 95% CI in monotherapy (29).

Chi-square test as univariate analysis and multiple logistic regression analysis were used to assess the risk of nephritis in ICPI monotherapy. Two-sided *p*-values less than 0.05 were considered significant. We conducted the multiple logistic regression analysis in ICPI dataset showing significant ADE signals of nephritis. Multiple logistic regression analysis in each ICPI dataset was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics and ROR of monotherapy. A total of 591,114 cases were included in the dataset (Figure 1). The numbers of side-effects associated with nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, and avelumab were 9,116, 5,838, 2,831, 1,288, 1,054, and 48, respectively (Table III). In patients taking ICPI monotherapy, ADE signals of nephritis were detected in the atezolizumab, ipilimumab, durvalumab, nivolumab, and pembrolizumab groups. The use of atezolizumab [ROR (95% CI)=1.780 (1.102 to 2.874)], ipilimumab [ROR (95% CI)=2.454 (1.857 to 3.242)], nivolumab [ROR (95% CI)=2.091 (1.764 to 2.479)], and pembrolizumab [ROR (95% CI)=2.443 (2.008 to 2.973)] showed a statistically significant signal for nephritis (Table IV). Although the durvalumab group also showed ADE signals for nephritis, the signals were not statistically significant [ROR (95% CI)=0.252 (0.063 to 1.010)] (Table IV). Moreover, the avelumab group did not show any ADE signal for nephritis because of the small sample size.

ADE signals of nephritis were detected in patients treated with PPIs. The use of esomeprazole [ROR (95% CI)=2.064 (1.326 to 3.214)], omeprazole [ROR (95% CI)=4.248 (3.209 to 5.622)], vonoprazan [ROR (95% CI)=1.829 (1.132 to 2.954)], rabeprazole [ROR (95% CI)=3.169 (2.263 to 4.437)], and lansoprazole [ROR (95% CI)=2.178 (1.705 to 2.783)] showed a statistically significant signal for nephritis (Table IV).

Drug-drug interaction signals. The signals of drug-drug interactions are shown in Table IV. Cases with concomitant use of atezolizumab and rabeprazole [ROR (95% CI)=66.43 (6.022 to 732.8)], ipilimumab and omeprazole [ROR (95% CI)=265.8 (24.09 to 2931)], ipilimumab and lansoprazole [ROR (95% CI)=29.53 (6.378 to 136.7)], nivolumab and esomeprazole [ROR (95% CI)=40.91 (13.33 to 125.5)], nivolumab and omeprazole [ROR (95% CI)=199.5 (56.28 to 707.3)], nivolumab and rabeprazole [ROR (95% CI)=114.0 (38.30 to 339.4)], nivolumab and lansoprazole [ROR (95% CI)=31.04 (13.67 to 70.71)], pembrolizumab and esomeprazole [ROR

Table I. *Preferred terms to define different cancer types (appearing in the Medical Dictionary for Regulatory Activities version 23.1).*

Cancer type	Preferred terms number	Preferred terms
Non-small cell lung cancer	10001245	Adenosquamous cell lung cancer
	10001247	Adenosquamous cell lung cancer recurrent
	10001248	Adenosquamous cell lung cancer stage 0
	10001249	Adenosquamous cell lung cancer stage I
	10001250	Adenosquamous cell lung cancer stage II
	10001251	Adenosquamous cell lung cancer stage III
	10001254	Adenosquamous cell lung cancer stage IV
	10023775	Large cell lung cancer recurrent
	10023776	Large cell lung cancer stage 0
	10023777	Large cell lung cancer stage I
	10023778	Large cell lung cancer stage II
	10023779	Large cell lung cancer stage III
	10023780	Large cell lung cancer stage IV
	10025031	Lung adenocarcinoma
	10025033	Lung adenocarcinoma recurrent
	10025034	Lung adenocarcinoma stage 0
	10025035	Lung adenocarcinoma stage I
	10025036	Lung adenocarcinoma stage II
	10025037	Lung adenocarcinoma stage III
	10025038	Lung adenocarcinoma stage IV
	10025120	Lung squamous cell carcinoma recurrent
	10025121	Lung squamous cell carcinoma stage 0
	10025122	Lung squamous cell carcinoma stage I
	10025123	Lung squamous cell carcinoma stage II
	10025124	Lung squamous cell carcinoma stage III
	10025125	Lung squamous cell carcinoma stage IV
	10029515	Non-small cell lung cancer recurrent
	10029516	Non-small cell lung cancer stage 0
	10029517	Non-small cell lung cancer stage I
	10029518	Non-small cell lung cancer stage II
	10029519	Non-small cell lung cancer stage III
	10029520	Non-small cell lung cancer stage IIIA
	10029521	Non-small cell lung cancer stage IIIB
	10029522	Non-small cell lung cancer stage IV
	10061873	Non-small cell lung cancer
	10069730	Large cell lung cancer metastatic
	10071533	Lung squamous cell carcinoma metastatic
	10059515	Non-small cell lung cancer metastatic
Head and neck cancer	10071540	Head and neck cancer metastatic
	10067821	Head and neck cancer
	10071539	Head and neck cancer stage I
	10071538	Head and neck cancer stage II
	10071537	Head and neck cancer stage III
	10071536	Head and neck cancer stage IV
	10060121	Squamous cell carcinoma of head and neck
Urothelial cancer	10004986	Bladder adenocarcinoma recurrent
	10004987	Bladder adenocarcinoma stage 0
	10004988	Bladder adenocarcinoma stage I
	10004989	Bladder adenocarcinoma stage II
	10004990	Bladder adenocarcinoma stage III
	10004991	Bladder adenocarcinoma stage IV
	10004992	Bladder adenocarcinoma stage unspecified
	10005003	Bladder cancer
	10005005	Bladder cancer recurrent
	10005006	Bladder cancer stage 0, with cancer *in situ*
	10005008	Bladder cancer stage I, with cancer *in situ*
	10005010	Bladder cancer stage II
	10005011	Bladder cancer stage III
	10005012	Bladder cancer stage IV
	10005075	Bladder squamous cell carcinoma recurrent
	10005076	Bladder squamous cell carcinoma stage 0
	10005077	Bladder squamous cell carcinoma stage I
	10005078	Bladder squamous cell carcinoma stage II
	10005079	Bladder squamous cell carcinoma stage III
	10005080	Bladder squamous cell carcinoma stage IV
	10005081	Bladder squamous cell carcinoma stage unspecified
	10005084	Bladder transitional cell carcinoma
	10057352	Metastatic carcinoma of the bladder
	10066749	Bladder transitional cell carcinoma stage 0
	10066750	Bladder transitional cell carcinoma recurrent
	10066751	Bladder transitional cell carcinoma stage I
	10066752	Bladder transitional cell carcinoma stage IV
	10066753	Bladder transitional cell carcinoma stage II
	10066754	Bladder transitional cell carcinoma stage III
	10071664	Bladder transitional cell carcinoma metastatic
	10078341	Neuroendocrine carcinoma of the bladder
	10026426	Malignant neoplasm of renal pelvis
	10044406	Transitional cell cancer of renal pelvis and ureter metastatic
	10044407	Transitional cell cancer of the renal pelvis and ureter
	10044408	Transitional cell cancer of the renal pelvis and ureter localised
	10044410	Transitional cell cancer of the renal pelvis and ureter recurrent
	10044411	Transitional cell cancer of the renal pelvis and ureter regional
	10046392	Ureteric cancer
	10046393	Ureteric cancer local
	10046394	Ureteric cancer metastatic
	10046396	Ureteric cancer recurrent
	10046397	Ureteric cancer regional
	10026326	Malignant neoplasm of paraurethral glands
	10044412	Transitional cell carcinoma
	10044426	Transitional cell carcinoma urethra
	10046431	Urethral cancer
	10046433	Urethral cancer metastatic
	10046435	Urethral cancer recurrent
	10061272	Malignant urinary tract neoplasm
	10061396	Urinary tract carcinoma in situ
	10071080	Transitional cell carcinoma metastatic
	10074419	Malignant genitourinary tract neoplasm
	10077051	Transitional cell carcinoma recurrent
	10005056	Bladder neoplasm

Table I. *Continued*

Table I. *Continued*.

Cancer type	Preferred terms number	Preferred terms
	10061398	Urinary tract neoplasm
	10062221	Ureteral neoplasm
	10062223	Urethral neoplasm
Renal cell carcinoma	10009253	Clear cell sarcoma of the kidney
	10029145	Nephroblastoma
	10038389	Renal cancer
	10038390	Renal cancer recurrent
	10038391	Renal cancer stage I
	10038392	Renal cancer stage II
	10038393	Renal cancer stage III
	10038394	Renal cancer stage IV
	10038410	Renal cell carcinoma recurrent
	10038411	Renal cell carcinoma stage I
	10038412	Renal cell carcinoma stage II
	10038413	Renal cell carcinoma stage III
	10038414	Renal cell carcinoma stage IV
	10039019	Rhabdoid tumour of the kidney
	10050018	Renal cancer metastatic
	10050176	Renal oncocytoma
	10050513	Metastatic renal cell carcinoma
	10051948	Renal adenoma
	10061482	Renal neoplasm
	10061872	Non-renal cell carcinoma of kidney
	10067943	Hereditary papillary renal carcinoma
	10067944	Hereditary leiomyomatosis renal cell carcinoma
	10067946	Renal cell carcinoma
	10069908	Renal haemangioma
	10073251	Clear cell renal cell carcinoma
	10078493	Papillary renal cell carcinoma
	10080544	Chromophobe renal cell carcinoma
	10081895	Multilocular cystic nephroma
	10083207	Renal hamartoma
Melanoma	10025650	Malignant melanoma
	10025652	Malignant melanoma in situ
	10025668	Malignant melanoma stage I
	10025669	Malignant melanoma stage II
	10025670	Malignant melanoma stage III
	10025671	Malignant melanoma stage IV
	10027480	Metastatic malignant melanoma
Gastric cancer	10001150	Adenocarcinoma gastric
	10017758	Gastric cancer
	10017761	Gastric cancer recurrent
	10017762	Gastric cancer stage 0
	10017763	Gastric cancer stage I
	10017764	Gastric cancer stage II
	10017765	Gastric cancer stage III
	10055008	Gastric sarcoma
	10061967	Gastric cancer stage IV
	10062878	Gastrooesophageal cancer
	10063916	Metastatic gastric cancer
	10066896	HER2 positive gastric cancer
	10081398	Gastrooesophageal cancer recurrent
Hodgkin lymphoma	10020208	Hodgkin's disease lymphocyte depletion stage I site unspecified
	10020209	Hodgkin's disease lymphocyte depletion stage I subdiaphragm
	10020210	Hodgkin's disease lymphocyte depletion stage I supradiaphragm
	10020211	Hodgkin's disease lymphocyte depletion stage II site unspecified
	10020212	Hodgkin's disease lymphocyte depletion stage II subdiaphragm
	10020213	Hodgkin's disease lymphocyte depletion stage II supradiaphragm
	10020215	Hodgkin's disease lymphocyte depletion type recurrent
	10020216	Hodgkin's disease lymphocyte depletion type refractory
	10020217	Hodgkin's disease lymphocyte depletion type stage III
	10020218	Hodgkin's disease lymphocyte depletion type stage IV
	10020219	Hodgkin's disease lymphocyte depletion type stage unspecified
	10020220	Hodgkin's disease lymphocyte predominance stage I site unspec
	10020221	Hodgkin's disease lymphocyte predominance stage I subdiaphragm
	10020222	Hodgkin's disease lymphocyte predominance stage I supradiaphragm
	10020223	Hodgkin's disease lymphocyte predominance stage II site unspec
	10020224	Hodgkin's disease lymphocyte predominance stage II subdiaphragm
	10020225	Hodgkin's disease lymphocyte predominance stage II supradiaphragm
	10020227	Hodgkin's disease lymphocyte predominance type recurrent
	10020228	Hodgkin's disease lymphocyte predominance type refractory
	10020229	Hodgkin's disease lymphocyte predominance type stage III
	10020230	Hodgkin's disease lymphocyte predominance type stage IV
	10020231	Hodgkin's disease lymphocyte predominance type stage unspecified
	10020206	Hodgkin's disease
	10020266	Hodgkin's disease recurrent
	10020267	Hodgkin's disease refractory
	10020268	Hodgkin's disease stage I
	10020269	Hodgkin's disease stage II
	10020270	Hodgkin's disease stage III
	10020271	Hodgkin's disease unclassifiable
	10061597	Hodgkin's disease stage IV
	10020233	Hodgkin's disease mixed cellularity recurrent
	10020234	Hodgkin's disease mixed cellularity refractory
	10020235	Hodgkin's disease mixed cellularity stage I site unspecified

Table I. *Continued*

Table I. *Continued*.

Cancer type	Preferred terms number	Preferred terms
	10020236	Hodgkin's disease mixed cellularity stage I subdiaphragmatic
	10020237	Hodgkin's disease mixed cellularity stage I supradiaphragmatic
	10020238	Hodgkin's disease mixed cellularity stage II subdiaphragmatic
	10020239	Hodgkin's disease mixed cellularity stage II supradiaphragmatic
	10020240	Hodgkin's disease mixed cellularity stage III
	10020241	Hodgkin's disease mixed cellularity stage IV
	10020242	Hodgkin's disease mixed cellularity stage unspecified
	10020244	Hodgkin's disease nodular sclerosis
	10020245	Hodgkin's disease nodular sclerosis recurrent
	10020246	Hodgkin's disease nodular sclerosis refractory
	10020252	Hodgkin's disease nodular sclerosis stage III
	10020253	Hodgkin's disease nodular sclerosis stage IV
	10073534	Hodgkin's disease nodular sclerosis stage II
	10073535	Hodgkin's disease nodular sclerosis stage I
Mesothelioma	10027406	Mesothelioma
	10027407	Mesothelioma malignant
	10027411	Mesothelioma malignant recurrent
	10034480	Pericardial mesothelioma malignant recurrent
	10034671	Peritoneal mesothelioma malignant recurrent
	10035603	Pleural mesothelioma
	10035607	Pleural mesothelioma malignant recurrent
	10056558	Peritoneal mesothelioma malignant
	10059518	Pleural mesothelioma malignant
	10073062	Biphasic mesothelioma
	10073063	Desmoplastic mesothelioma
	10073064	Epithelioid mesothelioma
	10073065	Sarcomatoid mesothelioma
	10073066	Pericardial mesothelioma malignant
Myeloma	10035222	Plasma cell leukaemia
	10035226	Plasma cell myeloma
	10035484	Plasmacytoma
	10053869	POEMS syndrome
	10060406	Plasma cell leukaemia in remission
	10073132	Plasma cell myeloma in remission
	10073133	Plasma cell myeloma recurrent
	10078282	Leptomeningeal myelomatosis
	10081847	Plasma cell myeloma refractory
Merkel cell carcinoma	10029266	Neuroendocrine carcinoma of the skin

HER2: Human epidermal growth factor receptor 2; POEMS: polyneuropathy, organomegaly, endocrinopathy, m-protein, and skin changes syndrome.

Table II. *Preferred terms to define nephritis as an immune-related adverse event (appearing in the Medical Dictionary for Regulatory Activities version 23.1)*.

Preferred terms number	Preferred terms
10018364	Glomerulonephritis
10018366	Glomerulonephritis acute
10018367	Glomerulonephritis chronic
10018370	Glomerulonephritis membranoproliferative
10018376	Glomerulonephritis proliferative
10018378	Glomerulonephritis rapidly progressive
10029120	Nephritis allergic
10029164	Nephrotic syndrome
10065673	Nephritic syndrome
10066453	Mesangioproliferative glomerulonephritis
10067757	Focal segmental glomerulosclerosis
10073016	Chronic autoimmune glomerulonephritis
10075626	Paraneoplastic nephrotic syndrome
10076749	Paraneoplastic glomerulonephritis
10029117	Nephritis
10048302	Tubulointerstitial nephritis
10069034	Tubulointerstitial nephritis and uveitis syndrome
10077087	Autoimmune nephritis
10083070	Immune-mediated nephritis
10020586	Hypercalcaemic nephropathy
10029151	Nephropathy
10037111	Pseudo-Bartter syndrome
10038457	Renal glycosuria
10038535	Renal tubular acidosis
10038536	Renal tubular atrophy
10038537	Renal tubular disorder
10050335	Renal tubular dysfunction
10050839	Bartter's syndrome
10051920	Glomerulonephropathy
10052313	Liddle's syndrome
10052607	Fanconi syndrome acquired
10054832	Diffuse mesangial sclerosis
10061989	Glomerulosclerosis
10062906	Gitelman's syndrome
10075849	Potassium wasting nephropathy
10080593	Pseudohypoaldosteronism
10083522	Immune-mediated renal disorder

(95% CI)=33.23 (9.374 to 117.8)], and pembrolizumab and lansoprazole [ROR (95% CI)=15.63 (3.611 to 67.69)] had a significantly higher ROR than monotherapy cases.

Multiple logistic regression analysis. In univariate analysis, the frequency of nephritis was significantly high in male patients treated with ipilimumab (OR=3.844; 95%CI=1.634-9.042; p=0.001). There were no significant differences in male patients treated with atezolizumab (OR=3.139; 95% CI=0.714-13.794; p=0.110), nivolumab (OR=1.371; 95% CI=0.913-2.060; p=0.126), and pembrolizumab (OR=1.648; 95% CI=0.977-2.782; p=0.059). We also conducted multiple

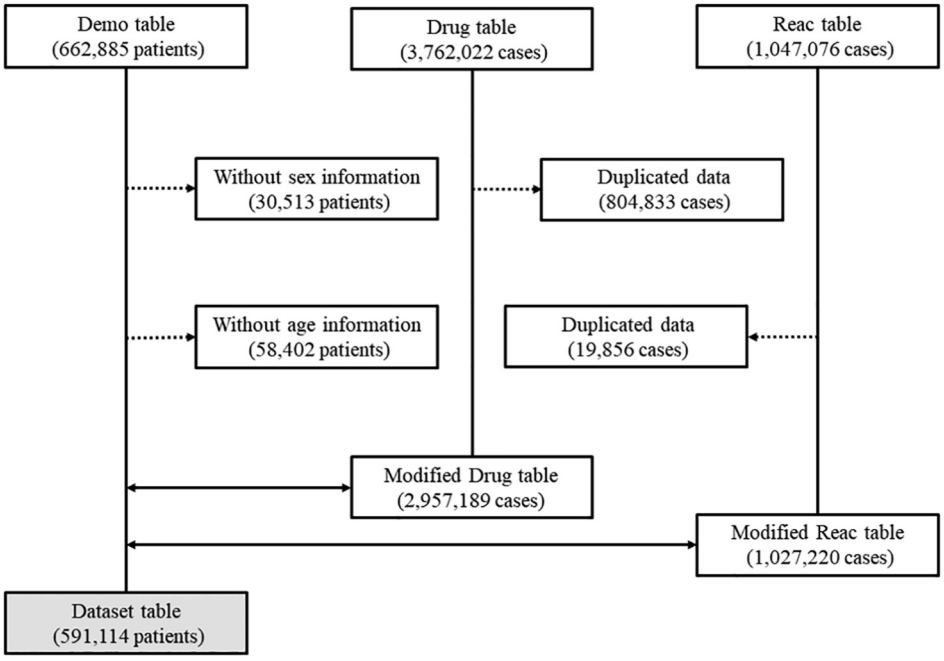

Figure 1. *Flow diagram of the study. Dotted arrow and double arrow show data exclusion and combination, respectively.*

Table III. *Patient characteristics*.

	Anti PD-1		Anti CTLA-4	Anti PD-L1		
Total N	Nivolumab (n=9,116)	Pembrolizumab (n=5,838)	Ipilimumab (n=2,831)	Atezolizumab (n=1,288)	Durvalumab (n=1,054)	Avelumab (n=48)
Gender Male (N)	6,626	4,424	1,883	911	849	27
Age ≥70 years old (N)	3,990	3,241	1,142	624	550	32
With PPI use						
Esomeprazole (N)	17	15	7	3	1	0
Omeprazole (N)	10	1	3	0	0	0
Vonoprazan (N)	12	13	3	10	1	0
Rabeprazole (N)	13	5	2	3	0	0
Lansoprazole (N)	37	19	11	4	3	0

PD-1: Programmed cell death protein 1; PD-L1: programmed cell death-ligand 1; CTLA: cytotoxic T-lymphocyte-associated protein; PPI: proton pump inhibitor.

logistic regression analysis to assess the risk of ipilimumab-induced nephritis. The frequency of nephritis was significantly higher in male patients treated with ipilimumab (OR=3.798; 95% CI=1.614-8.938; p=0.002). Age over 70 years did not influence the frequency of nephritis (Table V).

Discussion

The estimated incidence of ICPI-induced nephritis is much lower than that of other irAEs (26). Therefore, understanding ICPI-induced nephritis was limited to small case series. To clearly identify the risk factors for ICPI-induced nephritis, Cortazar *et al*. (13) conducted a multicenter study involving 138 patients with ICPI-induced nephritis. This report identified low baseline eGFR and PPI use as independent risk factors of ICPI-induced nephritis. However, the PPIs that increase the risk of ICPI-induced nephritis were not identified in this study. In the present study, omeprazole increased the frequency of nephritis in patients treated with ipilimumab or nivolumab. Esomeprazole and lansomeprazole increased the frequency of nivolumab and pembrolizumab-induced nephritis. Furthermore, the frequency of ipilimumab-induced nephritis increased in male patients.

Table IV. *Crude reporting odds ratios for nephritis.*

Concomitant drug	Drug	Case of nephritis	Total SE	ROR (95%CI)
Monotherapy	Atezolizumab	17	1,288	1.780 (1.102-2.874)
	Avelumab	0	48	N.A
	Ipilimumab	51	2,831	2.454 (1.857-3.242)
	Durvalumab	2	1,054	0.252 (0.063-1.010)
	Nivolumab	139	9,116	2.091 (1.764-2.479)
	Pembrolizumab	104	5,838	2.443 (2.008-2.973)
	Esomeprazole	20	1,310	2.064 (1.326-3.214)
	Omeprazole	51	1,660	4.248 (3.209-5.622)
	Vonoprazan	17	1,254	1.829 (1.132-2.954)
	Rabeprazole	35	1,510	3.169 (2.263-4.437)
	Lansoprazole	66	4,123	2.178 (1.705-2.783)
Atezolizumab	Esomeprazole	0	3	N.A
	Omeprazole	0	0	N.A
	Vonoprazan	1	10	14.76 (1.870-116.5)
	Rabeprazole	1	3	66.43 (6.022-732.8)
	Lansoprazole	0	4	N.A
Avelumab	Esomeprazole	0	0	N.A
	Omeprazole	0	0	N.A
	Vonoprazan	0	0	N.A
	Rabeprazole	0	0	N.A
	Lansoprazole	0	0	N.A
Ipilimumab	Esomeprazole	0	7	0
	Omeprazole	2	3	265.8 (24.09-2931)
	Vonoprazan	0	3	0
	Rabeprazole	0	2	0
	Lansoprazole	2	11	29.53 (6.378-136.7)
Durvalumab	Esomeprazole	0	1	N.A
	Omeprazole	0	0	N.A
	Vonoprazan	0	1	N.A
	Rabeprazole	0	0	N.A
	Lansoprazole	0	3	N.A
Nivolumab	Esomeprazole	4	17	40.91 (13.33-125.5)
	Omeprazole	6	10	199.5 (56.28-707.3)
	Vonoprazan	0	12	N.A
	Rabeprazole	6	13	114.0 (38.30-339.4)
	Lansoprazole	7	37	31.04 (13.67-70.71)
Pembrolizumab	Esomeprazole	3	15	33.23 (9.374-117.8)
	Omeprazole	0	1	N.A
	Vonoprazan	0	13	N.A
	Rabeprazole	1	5	33.21 (3.711-297.2)
	Lansoprazole	2	19	15.63 (3.611-67.69)

SE: Side effect; ROR: reporting odds ratio; CI: confidence interval; N.A: not available.

Hypomagnesemia, AKI, AIN, and CKD were reported as adverse events associated with PPI use (30, 31). The risk of hospital admission was elevated within 120 days of PPI exposure (32). In addition, PPI use was associated with increasing mortality due to cardiovascular disease, CKD, and upper gastrointestinal cancer (33). These previous reports suggested that medical practitioners should consider the potential benefits and risks of PPIs. Based on kidney biopsy results, the frequency of AIN with severe inflammatory cell infiltration was higher in ICPI-induced nephritis than in other types of renal injury (14). Hence, these reports suggest that cell-mediated immunity is associated with nephritis. Although the underlying mechanism of PPI-induced nephritis is unclear, PPI-induced nephritis showed cellular infiltrates with lymphocytes and occasional eosinophils in the renal interstitium (20, 22). Therefore, concomitant use of ICPI and PPI might develop cell-mediated immunity associated with AIN. In the present study, omeprazole and lansoprazole showed high risk of nephritis induction in the cases with or without ICPI. Although the most of omeprazole-induced nephritis are recognized as interstitial damage (17, 30), the underlying mechanism is unclear.

Table V. *Univariate and multivariate analysis for predictors of ICPI-induced nephritis.*

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*p*-Value	OR (95%CI)	*p*-Value
Atezolizumab				
Male	3.139 (0.714-13.79)	0.110		
≥70 years	1.200 (0.460-3.130)	0.709		
Ipilimumab				
Male	3.844 (1.634-9.042)	0.001	3.798 (1.614-8.938)	0.002
≥70 years	1.432 (0.822-2.492)	0.202	1.386 (0.795-2.415)	0.250
Nivolumab				
Male	1.371 (0.913-2.060)	0.126		
≥70 years	0.975 (0.695-1.368)	0.885		
Pembrolizumab				
Male	1.648 (0.977-2.782)	0.059		
≥70 years	0.934 (0.633-1.378)	0.730		

ICPI: Immune checkpoint inhibitor; OR: odds ratio; CI: confidence interval.

Organic cation transporters (OCTs) uptake PPIs to renal tubular cells (34). Since the affinity for OCTs and accumulation in renal tubular cells are higher for omeprazole or lansoprazole than that for rabeprazole (34), omeprazole, and lansoprazole have more potential in inducing AIN compared to other PPIs.

Male gender showed an increasing tendency towards risk of ICPI-induced nephritis (13). Although the mechanism of nephritis in male patients treated with ICPIs was unclear, our results supported this previous report. Since the frequency of irAEs is higher in female patients than that in male patients (35-37), ICPI-induced nephritis might have different mechanism to that of other irAEs. Since ipilimumab has an immunoglobulin G_1 (IgG_1) structure, it might lead to higher activation of complement and other immune system factors than the rest of the IgG subtypes (38-40). Therefore, our results suggested that male patients or patients with concomitant use of ICPIs and PPIs (excluded vonoprazan) should be monitored for renal function after chemotherapy.

The present study has certain limitations. First, the ADE signal of avelumab-induced nephritis was either weak or not detected because of the small sample size. Nivolumab was approved in Japan in 2014, whereas ipilimumab, pembrolizumab, avelumab, atezolizumab, and durvalumab were approved in 2016, 2015, 2017, 2018, and 2018, respectively. Therefore, the number of ADE reports for nivolumab is greater than those for the other ICPIs. Second, as a large spontaneous reporting system, the JADER database has various biases including under- or over-reporting and confounders caused by comorbidities (28, 41-45). Third, the number of nephritis event was small in concomitant use of ICPI and PPI. Although multiple logistic regression analysis could be conducted in monotherapy data set, this analysis was not applied for concomitant use data set because of lack statistical power.

The most common trigger of AIN is the drug used (46), therefore the identification of the types of drug is important in determining a preventive strategy. Although our results provide new insights of ICPI- and PPI-induced nephritis, further basic and clinical studies are required to elucidate the mechanisms of action.

Conflicts of Interest

The Authors report no conflicts of interest regarding this work.

Authors' Contributions

KK, TM, YI, and NT designed this study. KK and TK carried out the survey of the JADER database. KK, TM, TK, and MH performed the statistical analyses. KK, TM, YI, KT, SY, and NT drafted the manuscript. All Authors approved the final manuscript.

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