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Nephrotoxicity of Immune Checkpoint Inhibitors: A Disproportionality Analysis from 2013 to 2020

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Nephrotoxicity occasionally occurs during treatment with immune checkpoint inhibitors (ICIs). Few related studies compare the differences between these drugs. This study aimed to systematically characterize nephrotoxicity after ICI initiation. Data were extracted from the US FDA Adverse Event Reporting System (FAERS) database. Disproportionality analysis, including information components (ICs) and reporting odds ratios (RORs), was performed to determine the potential renal toxicity of ICIs. A total of 7,204 reports of renal adverse events (AEs) were identified in the FAERS database. Renal AEs were most commonly reported for nivolumab (46.84%). Strong signals were detected in male patients combined with ICIs. In the clinical application of ICIs, attention should be paid to patients, especially male patients, with acute kidney injury, nephritis, autoimmune nephritis and other nephrotoxic AEs. The use of ICIs is likely to aggravate their condition.

Keywords: adverse events; Adverse Event Reporting System; disproportionality analysis; immune checkpoint inhibitors; nephrotoxicity
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Introduction

Immune checkpoint inhibitors (ICIs) are a novel class of medications in the treatment of cancer. They have rapidly obtained a popularity for their success in improving clinical outcomes in a great many cancer types (Wrangle et al. 2018). The immune checkpoints programmed cell death protein 1 pathway (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) acted as a "brake" role in immune function, and suggested that immune checkpoint inhibition may reactivate T cells and eliminate cancer cells effectively (Ljunggren et al. 2018).

Accumulating evidence indicates that the inhibition of PD-1 promotes an effective immune response against cancer cells (Messenheimer et al. 2017). In addition, the development of PD-L1 checkpoint inhibitors has changed the landscape of non-small-cell lung cancer (NSCLC) therapy, with 2 approvals from the US Food and Drug Administration (FDA) of PD-1 inhibitors for second-line therapy (Sacher and Gandhi 2016). About the clinical manifestations of CTLA-4, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level (Hellmann et al. 2019).

However, the risk of adverse events (AEs) of ICIs has attracted attention in clinical practice. Nephrotoxicity is one very common AE. It may induce serious and fatal events if doctors do not recognize and treat it promptly. Renal immune-related adverse events are rare, with an estimated incidence of 2% with anti-PD-1/PD-L1 and 5% with combination therapy in a review of published phase 2 and 3 trials, but more recent studies have suggested that the incidence of acute kidney injury is higher than that initially reported (Li et al. 2021).

In this study, a disproportionality analysis was con-

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ducted to characterize and evaluate nephrotoxicity associated with ICI regimens using AE data in the FDA Adverse Event Reporting System (FAERS) database. Although the data in FAERS database may lack detailed clinical information, this approach may help discover potential drug-toxicity associations.

Materials and Methods

Study design and data sources

This retrospective, pharmacovigilance study is a disproportionality analysis based on the FAERS database, a collection of reports of AEs by consumers, healthcare providers, drug manufacturers, and others. It allows for the signal detection and quantification of the association between drugs and the reports of AEs (Min et al. 2018). Input data for this study were taken from the public release of the FAERS database, covering the period from the first quarter of 2013 to the second quarter of 2020.

Procedure

The drugs studied included antibodies targeting PD-1 (nivolumab and pembrolizumab), PD-L1 (atezolizumab, avelumab and durvalumab), and CTLA-4 (ipilimumab and tremelimumab). Generic names and brand names were used to identify the records associated with the ICIs because there is no uniform coding system for medications.

This study included all renal disorders (excluding nephropathies) (Medical Dictionary for Regulatory Activities (MedDRA) code 10038430) and all nephropathies (MedDRA code 10029149) according to MedDRA version 23.0. In the FAERS database, each report is coded using the preferred terms (PTs) from MedDRA, the international medical terminology developed by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Statistical analysis

Disproportionality appears when a drug is associated with a specific AE in pharmacovigilance studies. Two-by-two contingency tables were used to count the AE reports of the suspected drugs and other drugs (Table 1). Two data mining methods, reporting odds ratios (RORs) and Bayesian confidence propagation neural networks (BCPNNs) of information components (ICs), were used to calculate disproportionality.

The ROR can be expressed as (Stricker and Tijssen 1992)

$$ROR = \frac{a/c}{b/d} = \frac{ad}{bc}$$

The standard error of ln (ROR) and 95% confidence interval can be calculated by

$$SE\left(lnROR\right) = \sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}$$

$$95\%CI = e^{\ln(ROR)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

The BCPNN and its variance can be calculated as (Weinstein et al. 2009)

$$E\left(IC_{ij}\right) = \log_2 \frac{\left(c_{ij}+\gamma_{ij}\right)\left(C+\alpha\right)\left(C+\beta\right)}{\left(C+\gamma\right)\left(c_i+\alpha_i\right)\left(c_j+\beta_j\right)}$$

$$V\left(IC_{ij}\right) = \frac{\frac{C-c_{ij}+\gamma-\gamma_{ij}}{\left(c_{ij}+\gamma_{ij}\right)\left(1+C+\gamma\right)} + \frac{C-c_i+\alpha-\alpha_i}{\left(c_i+\alpha_i\right)\left(1+C+\alpha\right)} + \frac{C-c_j+\beta-\beta_i}{\left(c_i+\beta_j\right)\left(1+C+\beta\right)}}{\left(\log 2\right)^2}$$

where

$$\gamma = \gamma_{ij}\frac{\left(C+\alpha\right)}{\left(c_i+\alpha_i\right)}\cdot\frac{\left(C+\beta\right)}{\left(c_j+\beta_j\right)}$$

and $\gamma_{ij} = 1$, $\alpha_i = 1$, $\alpha = 2$, $\beta_j = 1$, and $\beta = 2$; C is the total number of reports in the database, C_{ij} is the number of combinations between the ICI drugs (i) and the nephrotoxicity reaction (j), C_i is the total number of reports on the ICI drugs (i) in the database and C_j is the total number of reports on the nephrotoxicity reaction (j) in the database.

The signal was considered significant if the lower limit of the 95% confidence interval (ROR025) was higher than 1, or if the lower end of the 95% confidence interval of information component (IC025) was greater than 0. All analyses were performed with SAS version 9.4 and R version 3.6.3. Ethics approval and consent to participate are not applicable.

Results

Descriptive analysis

A total of 52,583,692 records from the FAERS database were involved in this study, and 7,204 reports were AEs of nephrotoxicity after treatment with ICIs. The clinical characteristics of patients with kidney toxicity using ICIs are shown in Tables 2 and 3. Among all reports of nephrotoxicity associated with ICIs, the proportion of males was larger than that of females (63.66% vs. 29.96%). With further analysis, the signal was also detected (ROR025 = 2.32, IC025 = 0.49). Among all reports of nephrotoxicity associated with each ICI, the signal of males was larger than that of females (Table 4). Significant difference existed between different age groups, too. The proportion of the elderly (≥ 65) was larger than that of the non-elderly (< 65) (51.94% vs. 33.94%), and the difference was significant (ROR025 = 1.12, IC025 = 0.04), which might be attributed to degenerative change of the elderly. The most frequently reported severe outcomes were other serious medical events and hospitalization. Hospitalization (ROR025 = 2.18, IC025 = 0.79), death (ROR025 = 1.50, IC025 = 0.53) and life-threatening (ROR025 = 2.08, IC025 = 1.01) events associated with renal AEs after ICI treatment were reported, indicating the potentially life-threatening nature of ICI-related nephrotoxicity.

Table 1. 2*2 contingency tables for immune checkpoint inhibitor (ICI)-induced nephrotoxicity.

	Reports with nephrotoxicity	Reports without nephrotoxicity
Reports with the suspected drugs	a	b
All other reports	c	d

Table 2. Sex and age of patients with immune checkpoint inhibitor (ICI)-induced nephrotoxicity.

		Nephrotoxicity AEs with ICIs (7,204)	Nephrotoxicity AEs with any other drugs (1,726,412)	IC025	ROR025
Sex	Male	4,586 (63.66%)	620,114 (35.92%)	**0.49**	**2.32**
	Female	2,158 (29.96%)	710,231 (41.14%)	−0.80	0.39
	Transsex	5 (0.07%)	3,252 (0.19%)		
	Intersex	1 (0.01%)	3 (0.00%)		
	Unknown	0 (0.00%)	52 (0.00%)		
	MISS*	454 (6.30%)	392,760 (22.75%)		
Age	≥ 65	3,742 (51.94%)	599,649 (34.73%)	**0.04**	**1.12**
	< 65	2,445 (33.94%)	460,965 (26.70%)	−0.20	0.81
	MISS*	1,017 (14.12%)	665,798 (38.57%)		

Table 2 shows the clinical characteristics of patients with kidney toxicity using ICIs and any other drugs. The number and the percentage are shown.
*Missing value in FAERS database.
AEs, adverse events; IC025, the lower end of the 95% confidence interval of IC; ROR025, the lower limit of the 95% confidence interval of ROR; Empty cells; there are not enough data to compute.

Table 3. Outcome and country of patients with immune checkpoint inhibitor (ICI)-induced nephrotoxicity.

		Nephrotoxicity AEs with ICIs (6,668)	Nephrotoxicity AEs with any other drugs (1,726,948)	IC025	ROR025
Outcome	Other Serious	3,316 (46.03%)	1,130,623 (65.48%)	−0.57	0.38
	Hospitalization	2,430 (33.73%)	319,254 (18.49%)	**0.79**	**2.18**
	Death	545 (7.57%)	82,374 (4.77%)	**0.53**	**1.50**
	Life-threatening	256 (3.55%)	26,565 (1.54%)	**1.01**	**2.08**
	Disability	75 (1.04%)	21,843 (1.27%)	−0.62	0.65
	RI[&]	2 (0.03%)	969 (0.20%)		
	Congenital anomaly	1 (0.01%)	3,396 (0.06%)		
	MISS*	579 (8.04%)	141,388 (8.19%)		
Country	United States	1,876 (26.04%)	1,279,158 (74.09%)	−1.60	0.11
	Japan	1,602 (22.24%)	78,492 (4.55%)	**2.16**	**5.59**
	France	893 (12.40%)	73,415 (4.25%)	**1.40**	**2.92**
	Germany	505 (7.01%)	32,837 (1.90%)	**1.70**	**3.49**
	Spain	323 (3.69%)	17,611 (1.02%)	**1.91**	**4.01**
	United Kingdom	266 (4.48%)	41,645 (2.41%)	**0.41**	**1.35**
	Italy	193 (2.68%)	18,270 (1.06%)	**1.09**	**2.19**
	Australia	145 (2.01%)	8,750 (0.51%)	**1.68**	**3.36**

Table 3 shows the outcome and countries of patients with kidney toxicity using ICIs and any other drugs. The number and the percentage are shown.
[&]Required intervention to prevent permanent impairment/damage.
*Missing value in FAERS database.
AEs, adverse events; IC025, the lower end of the 95% confidence interval of IC; ROR025, the lower limit of the 95% confidence interval of ROR; Empty cells, there are not enough data to compute.

Table 4. The signals of patients' sex with immune checkpoint inhibitor (ICI)-induced nephrotoxicity.

	Sex	N	ROR	ROR025	IC	IC025
Atezolizumab	Male	466	2.33	**1.99**	1.44	**0.35**
	Female	229	0.43	0.37	0.62	−0.91
Avelumab	Male	62	8.88	**4.25**	1.90	**0.39**
	Female	8	0.11	0.05	0.22	−3.20
Cemiplimab	Male	6				
	Female	0				
Durvalumab	Male	183	1.58	**1.26**	1.24	**0.04**
	Female	133	0.64	0.51	0.79	−0.63
Ipilimumab	Male	567	2.27	**1.97**	1.43	**0.36**
	Female	281	0.43	0.38	0.62	−0.89
Nivolumab	Male	2261	3.02	**2.79**	1.55	**0.56**
	Female	859	0.33	0.31	0.52	−1.06
Pembrolizumab	Male	968	1.83	**1.65**	1.32	**0.28**
	Female	607	0.55	0.50	0.72	−0.60
Tremelimumab	Male	73	2.04	**1.39**	1.37	**0.01**
	Female	41	0.50	0.34	0.68	−1.09

Table 4 shows the signals of patients' sex with kidney toxicity using ICIs. Cemiplimab has little reports to find signals.
N, number of total records; ROR, reporting odds ratio; ROR025, the lower end of the 95% confidence interval of ROR; IC, information component; IC025, the lower end of the 95% confidence interval of IC.

Table 5. Frequency of nephrotoxic adverse events (AEs) related to immune checkpoint inhibitor (ICI) drugs.

Nephrotoxic AEs	N	Percentage
Acute kidney injury	2,404	33.37%
Renal failure	1,128	15.66%
Renal impairment	778	10.8%
Tubulointerstitial nephritis	617	8.56%
Nephritis	350	4.86%
Renal disorder	299	4.15%
Others*	1,628	22.53%

*Other nephrotoxic.
AEs; N, the number of records with kidney AEs reported for ICIs.

However, differences in various specific nephrotoxic AEs were observed in all ICI regimens. Among all the reports of AEs of nephrotoxicity, acute kidney injury (2,404, 33.37%), renal failure (1,128, 15.66%), renal impairment (778, 10.8%), tubulointerstitial nephritis (617, 8.56%), nephritis (350, 4.86%), and renal disorder (299, 4.15%) were the most frequently reported (Table 5). These reports account for 77.47% of the all the reports. The other reports of AEs of nephrotoxicity are considered rare.

The spectrum of nephrotoxicity AEs differs in immunotherapy regimens

In general, ICIs were hardly associated with renal AEs. When further analysis was done, there was significant difference between AEs related to nephrotoxicity and atezolizumab in total (IC025: 0.05; ROR025: 1.04), but not the other ICIs (Table 6).

Eleven preferred terms (PTs) were significantly associated with atezolizumab treatment, ranging from pyelonephritis (ROR025 = 1.20, IC025 = 0.07) to glomerulonephritis chronic (ROR025 = 51.95, IC025 = 1.17). Nivolumab was with a broadest spectrum of renal AEs with 26 PTs detected as signals, ranging from anuria (ROR025 = 1.02, IC025 = −0.03) to autoimmune nephritis (ROR025 = 29.03, IC025 = 3.46). Twenty-one PTs were significantly associated with pembrolizumab treatment, ranging from renal tubular necrosis (ROR025 = 1.06, IC025 = 0.04) to immune-mediated renal disorder (ROR025 = 185.22, IC025 = 1.69). Nine PTs were significantly associated with ipilimumab treatment, ranging from nephrotic syndrome (ROR025 = 1.08, IC025 = −0.04) to autoimmune nephritis (ROR025 = 72.67, IC025 = 3.77). For durvalumab, 7 disproportionality signals were detected, ranging from thrombotic microangiopathy (ROR025= 1.97, IC025 = 0.77) to autoimmune nephritis (ROR025 = 18.27, IC025 = 0.72). Small number of the other signals were reported. But some very strong signals were found. Avelumab was much stronger associated with pyelonephritis (ROR025 = 5.27, IC025 = 1.17). Cemiplimab was much stronger associated with autoimmune nephritis (ROR025 = 375.35, IC025 = 0.83) and kidney transplant rejection (ROR025 = 13.22, IC025 = 0.20). Tremelimumab was much stronger associated with nephritis (ROR025 = 27.90, IC025 = 2.83), etc (Figs. 1 and 2).

Discussion

Statistical analyses have been shown to be useful tools

Table 6. Association of total kidney adverse events (AEs) in total or class-specific immune checkpoint inhibitor (ICI) use

	(a)	(b)	(c)	(d)	ROR	ROR025	IC	IC025
Total	7,204	284,193	1,726,412	50,565,883	0.74	0.73	0.75	−0.45
Atezolizumab	718	18,739	1,707,673	50,856,562	1.12	**1.04**	1.12	**0.05**
Avelumab	77	2,680	1,723,732	50,857,203	0.84	0.67	0.85	−0.57
Cemiplimab	35	749	1,725,663	50,857,245	1.37	0.98	1.35	−0.08
Durvalumab	322	15,736	1,710,676	50,856,958	0.60	0.54	0.61	−0.88
Ipilimumab	915	47,794	1,678,618	50,856,365	0.56	0.53	0.57	−0.91
Nivolumab	3,374	130,976	1,595,436	50,853,906	0.76	0.73	0.76	−0.44
Pembrolizumab	1,649	63,475	1,662,937	50,855,631	0.76	0.73	0.77	−0.45
Tremelimumab	114	4,044	1,722,368	50,857,166	0.83	0.69	0.83	−0.54

Table 6 shows the information of total and specific ICI count in 2*2 contingency tables and calculation results by disproportionality analysis. The font will be bold if ROR025 is higher than 1 or IC025 is higher than 0.
(a) The number of records with kidney AEs reported for ICIs. (b) The number of records with any other AEs reported for ICIs. (c) The number of records with any kidney AEs for other drugs. (d) The number of records reported other AEs for other drugs. ROR, reporting odds ratio; ROR025, the lower end of the 95% confidence interval of ROR; IC, information component; IC025, the lower end of the 95% confidence interval of IC.

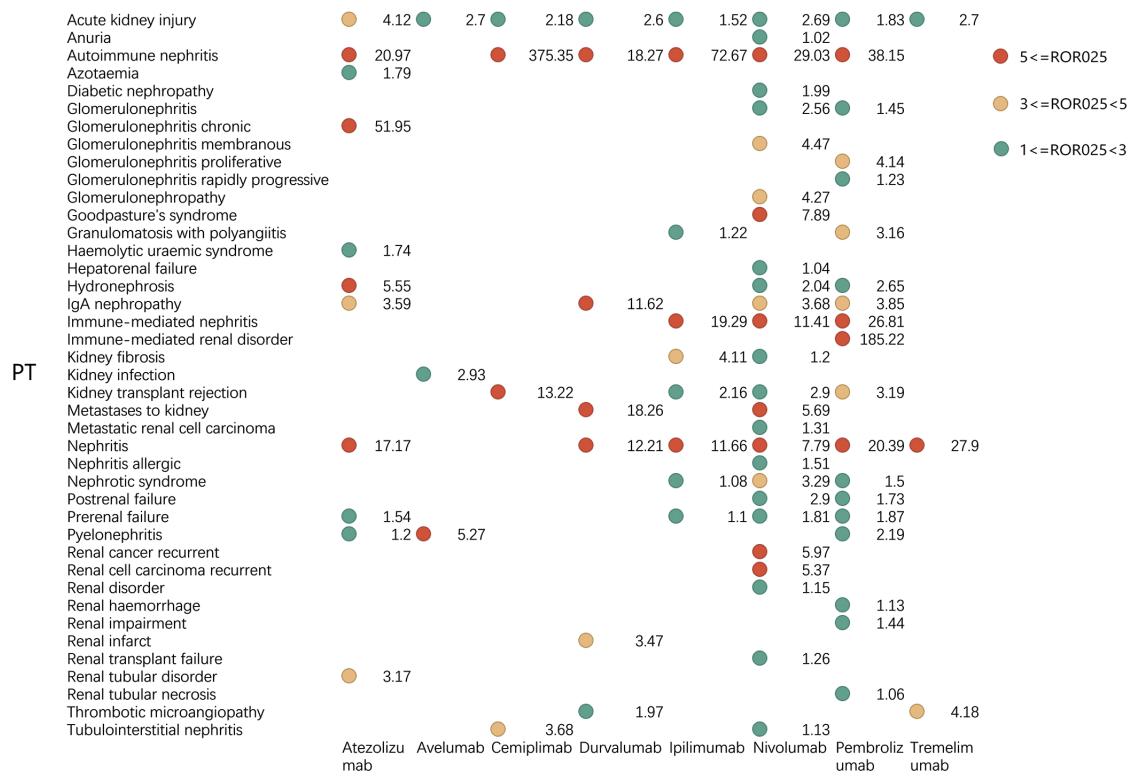

Fig. 1. All signals showing reporting odds ratios (RORs) of immune checkpoint inhibitor (ICI) drugs in detailed nephrotoxic adverse events (AEs).
PT, preferred term; ROR025, the lower end of the 95% confidence interval of ROR.
ROR025 greater than 1 was deemed a signal.

in aiding signal detection in spontaneous reporting systems. In previous study, the ROR was selected as the disproportionality analysis algorithms to characterize the spectrum, frequency, and clinical features of ICI-related adverse events (Raschi et al. 2019). However, no individual approach to detect signals is adequate and the concurrent use of other methods is essential (van Puijenbroek et al. 2002). Therefore, two methods, ROR and BCPNN, are used in this study. The selection of time intervals needs to pay attention to. In previous study, disproportionality and Bayesian analysis were used in data mining to screen the suspected renal adverse effects after the administration of different ICIs, based on FAERS from January 2004 to September 2019 (Chen et al. 2020). But the ICI relatively

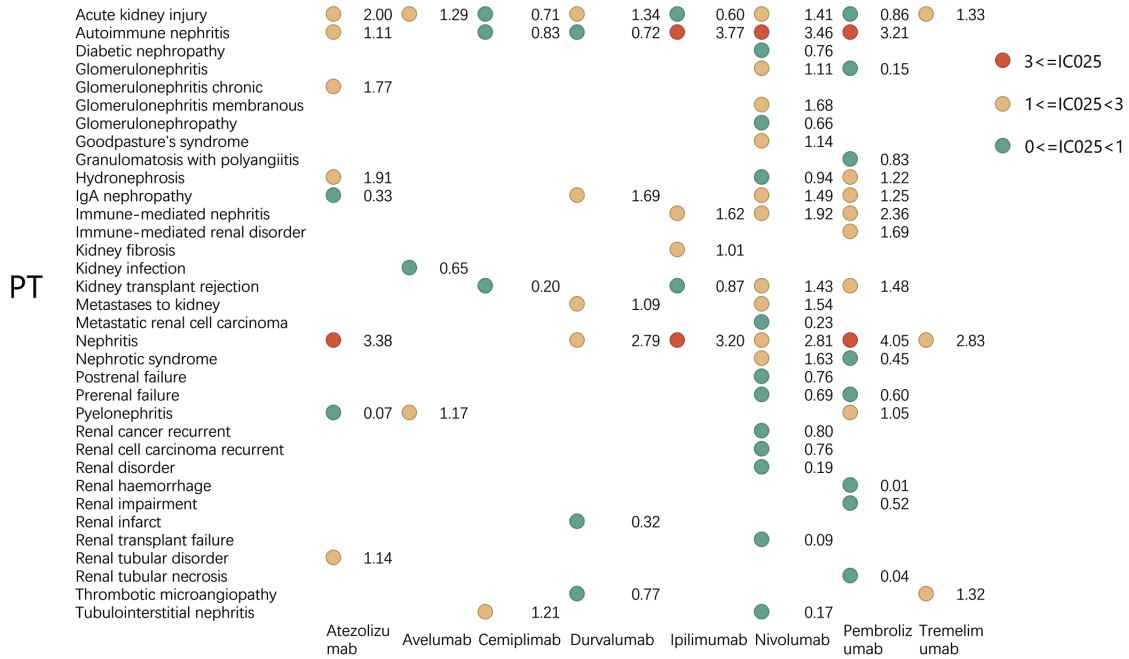

Fig. 2. All signals showing information components (ICs) of immune checkpoint inhibitor (ICI) drugs in detailed nephrotoxic adverse events (AEs).
PT, preferred term; IC025, the lower end of the 95% confidence interval of IC.
IC025 greater than 0 was deemed a signal.

larger market, ipilimumab, is listed in 2011. Redundant data increases the analysis results in probability errors. Our study is a pharmacovigilance study on ICI-associated nephrotoxicities based on more than 50 million records in the appropriate period of time. This makes our conclusion more stable compared with those of other studies.

Most clinical trials of ICIs have assessed clinical effects other than AEs and only given a short brief description of these severe or even fatal AEs. To the best of our knowledge, this study is the the most systematic and comprehensive collection until recently to compare the associations of renal adverse effects after different ICIs in the real-world practice based on the FAERS pharmacovigilance database. Previous researches show that ICIs can increase the risk of organ system toxicities such as endocrine, hematological, ear and labyrinth toxicity (Zhai et al. 2019; Hu et al. 2020; Ye et al. 2020). Nephrotoxicity is rare. Accounting for 2.47% among all ICI records with the latest data from January 1, 2013, to June 30, 2020.

Nephrotoxicity based on sex

Notably, compared with male patients, nephrotoxic AEs were reported more than those reported among female patients (63.66% vs. 29.96%). The result reflects that males are high-risky population to occur nephrotoxic AEs after treatment with ICI drugs. Previous research has also confirmed this (Chen et al. 2020). The reason for the difference of the occurring frequency of nephrotoxicity between males and females may be related to the level of sex hormones. Male hormones exert a deleterious effect in terms of increasing oxidative stress, activating the renin-angiotensin system, and worsening fibrosis within the damaged kidney, but female hormones exert a renoprotective effect (Valdivielso et al. 2019). Therefore, the clinical application of ICI drugs should focus on the occurrence of nephrotoxicity in male patients.

Association of total nephrotoxicity in total ICI use

The kidney is a vital organ for urine production, regulation of electrolytes and water, and homeostasis of nutrients and metabolites in the body (Liu et al. 2019). Medications are a relatively common cause of kidney injury (Markowitz and Perazella 2005; Perazella 2005, 2009, 2012; Uchino et al. 2007; Izzedine et al. 2009; Moffett and Goldstein 2011; Hoste et al. 2015). Drug-induced nephrotoxicity is more common in hospitalized patients, particularly intensive care unit patients (Mehta et al. 2004; Uchino et al. 2007; Moffett and Goldstein 2011; Hoste et al. 2015), and is affected by the inherent nephrotoxic potential of the drug, underlying patient characteristics that enhance the risk for kidney injury, and the metabolism and excretion of the potential offending agent by the kidney (Perazella 2003, 2005, 2009; Markowitz and Perazella 2005). The control group may express a higher proportion of renal toxicity. Also, ICI records may express too many other organ system toxicities, which may result in the expression of no significant association between renal AEs and ICIs.

Nephrotoxicity and atezolizumab

The kidney is composed of glomeruli and tubules. No

Table 7. Frequency of nephrotoxic adverse events (AEs) related to atezolizumab.

	Frequency	Percentage	Cumulative frequency	Cumulative percentage
Acute kidney injury	282	39.28%	282	39.28%
Renal failure	147	20.47%	429	59.75%
Renal impairment	58	8.08%	487	67.83%
Tubulointerstitial nephritis	48	6.69%	535	74.51%
Nephritis	36	5.01%	571	79.53%
Hydronephrosis	17	2.37%	588	81.89%
Chronic kidney disease	16	2.23%	604	84.12%
Renal disorder	12	1.67%	616	85.79%
Renal tubular disorder	11	1.53%	627	87.33%
Pyelonephritis	10	1.39%	637	88.72%
Thrombotic microangiopathy	9	1.25%	646	89.97%
Others*	72	10.03%	718	100.00%

*Other nephrotoxic AEs related to atezolizumab.

tendency of toxicity of each part is apparently in atezolizumab group (Table 7), which might be attributed to the mechanism of this drug. Atezolizumab is an engineered humanized monoclonal IgG1 antibody that binds selectively to PD-L1 and prevents its interaction with PD-1 and B7.1 while it is sparing the interaction between PD-L2 and PD-1. To some degree, atezolizumab may have higher appetency of the PD-L1 receptors that scattered over the kidney, which should be confirmed by more empirical studies.

Proven nephrotoxicity and ICIs

The results show that acute kidney injury, IgA nephropathy and nephritis show a significant difference with partial ICIs, and some of these signals were stronger than others (Fig. 2). This may be related to the mechanism of the ICIs. CTLA-4 is a part of the B7:CD28 immunoglobulin family found on the surface of T-cells and transmits an inhibitory signal to the T-cell. PD-1 is expressed on T-cells and binds to its ligands PD-L1 and PD-L2 that are expressed on cancer cells and other immune cells. Antibodies against PD-1, such as nivolumab, pembrolizumab and pidilizumab, or PD-L1, such as MEDI4736 and MPDL3280A increase the anti-tumor T-cell response by blocking the interaction of PD1 and PD-L1 to prevent T-cell inactivation (Curran et al. 2010). Acute kidney injury, IgA nephropathy and nephritis are complex diseases with many subtypes, and there are many causes of the disease (Cortazar et al. 2016; Mamlouk et al. 2019). Previous research has not been able to elaborate on the pathological mechanism. But what is certain is that changes in the immune system will affect other tissues, which is in line with the characteristics of the human body.

Autoimmune nephritis and ICIs

The results show that autoimmune nephritis and a variety of drugs are related, including atezolizumab (ROR025 = 20.97, IC025 = 1.11), cemiplimab (ROR025 = 375.35, IC025 = 0.83), ipilimumab (ROR025 = 72.67, IC025 = 3.77), durvalumab (ROR025 = 18.27, IC025 = 0.72), nivolumab (ROR025 = 29.03, IC025 = 3.46) and pembrolizumab (ROR025 = 38.15, IC025 = 3.21). It has not been mentioned in previous studies. Autoimmune nephritis disease is a disease caused by impaired autoimmune system. The aforementioned medicinal mechanism of the ICIs is very relevant with autoimmune nephritis. Therefore, medical staff must pay attention to the physical condition of such patients in clinical use.

Conclusion

This study comprehensively evaluated the association of ICIs and potential nephrotoxicities from real-world practice. Overall, no significant association was detected between ICIs and kidney AEs, while there was significant difference between AEs related to nephrotoxicity and atezolizumab in total. And class-specific nephrotoxicities were detected in several ICIs immunotherapy strategies. Partial results were consistent with previous literatures. The results show that acute kidney injury, IgA nephropathy and nephritis show a significant difference with partial ICIs. At the same time new discoveries have also emerged. Autoimmune nephritis and a variety of drugs are related, including atezolizumab, cemiplimab, ipilimumab, nivolumab and pembrolizumab. In the clinical application of ICIs, attention should be paid to patients, especially male patients and elderly patients, with acute kidney injury, nephritis, autoimmune nephritis and other nephrotoxic AEs. Related AEs of nephrotoxicity are warranted to be reminded by clinicians.

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Conflict of Interest

The authors declare no conflict of interest.

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