


ORIGINAL ARTICLE

# Risk factors associated with immune checkpoint inhibitor–induced acute kidney injury compared with other immune-related adverse events: a case–control study

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## ABSTRACT

**Background.** Immune checkpoint inhibitors (ICIs) foster anti-cancer immune responses. Their efficacy comes at the cost of immune-related adverse events (IRAEs). The latter affects various organs, including kidneys, mostly as acute tubulointerstitial nephritis, the pathophysiology of which remains unclear. We conducted a multicentre case–control study to compare the characteristics of patients with renal IRAEs (ICI-AKI) with those of patients diagnosed with other IRAEs.

**Methods.** We queried the French pharmacovigilance database for all adverse events involving ICIs. Reports were classified as ICI-AKI or extrarenal IRAE. For each ICI-AKI report, four reports of extrarenal IRAEs were randomly included (control group, 4:1 ratio). Variables showing an association with a  $P < 0.05$  were included as covariates in a multivariate analysis.

**Results.** Therefore, 167 ICI-AKI reports were compared with 668 extrarenal IRAEs. At least one concomitant extrarenal IRAE was mentioned in 44.3% of ICI-AKI reports. Patients with ICI-AKI were significantly older than patients with

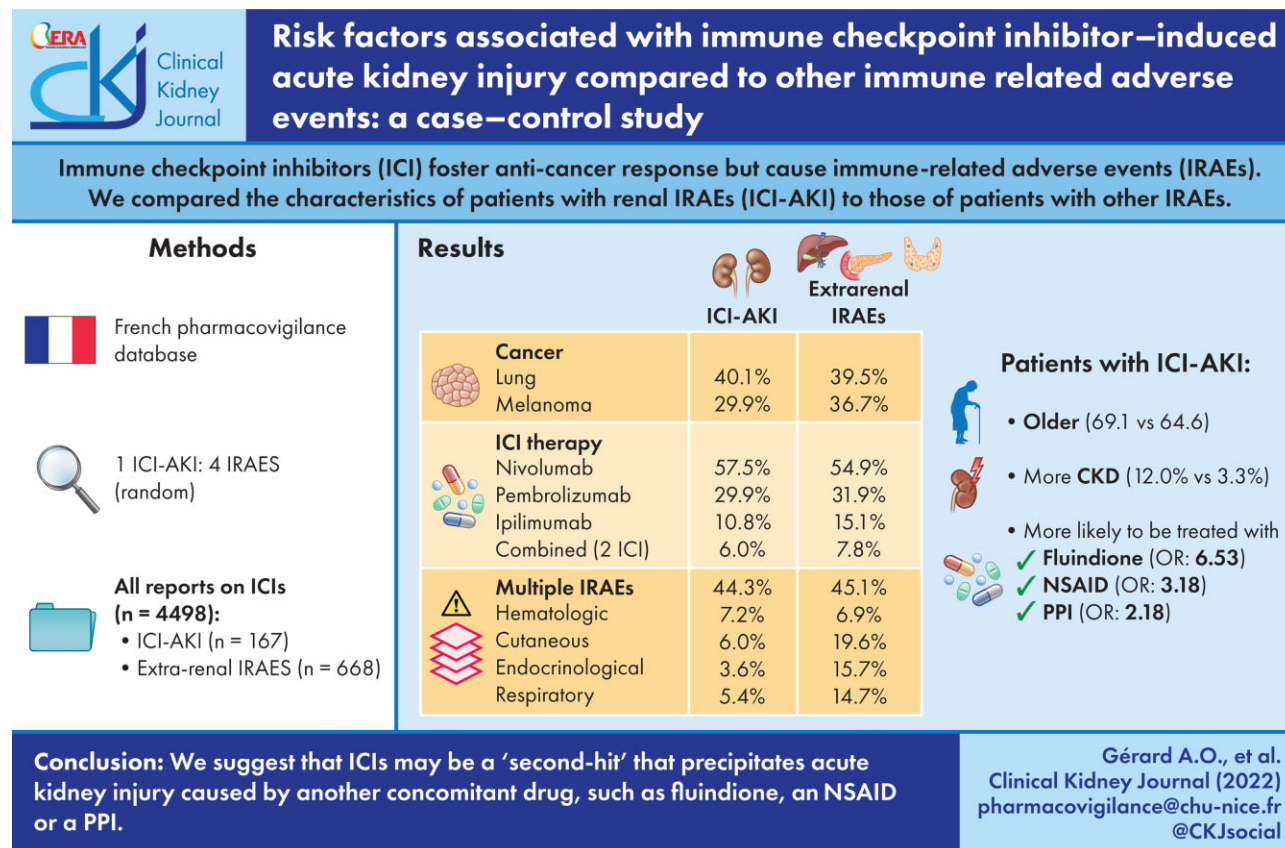
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extrarenal IRAEs (69.1 versus 64.6 years;  $P = 0.0135$ ), and chronic kidney disease was significantly more prevalent (12.0% versus 3.3%;  $P = 0.0125$ ). Patients with ICI-AKI were significantly more likely to be treated with fluindione [adjusted odds ratio (OR) 6.53, 95% confidence interval (95% CI) 2.21–19.31;  $P = 0.0007$ ], a non-steroidal anti-inflammatory drug (NSAID, OR 3.18, 95% CI 1.07–9.4;  $P = 0.0368$ ) or a proton-pump inhibitor (PPI, OR 2.18, 95% CI 1.42–3.34;  $P = 0.0004$ ).

**Conclusion.** This study is limited by a lack of data, preventing confirmation of numerous reports therefore not included in the analysis. We are unable to draw definite pathophysiological conclusions from our data. Nonetheless, we suggest that ICIs may be a ‘second-hit’ that precipitates acute kidney injury caused by another concomitant drug (fluindione, NSAID or PPI).

## GRAPHICAL ABSTRACT



**Keywords:** acute kidney injury, allergy, immune checkpoint inhibitors, immunotherapy, nephrology, nephrotoxicity, pharmacovigilance

## INTRODUCTION

Immune checkpoint inhibitors (ICIs) are a recent class of anti-cancer agents, intended to foster the physiological immune response against malignancies. Those ICIs target either cytotoxic T-lymphocyte-associated protein 4 (CTLA4, ipilimumab) or the programmed cell death protein 1 (PD1) pathway (nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab and durvalumab) [1].

This class has profoundly changed the management of a broad spectrum of advanced malignancies, including melanoma and lung cancer [2], so that the indications of ICIs keep expanding at a fast pace. However, ICIs are also associated with a specific array of immune-related adverse events (IRAEs) affecting various organs such as the skin, the gastrointestinal tract and the endocrine organs [3].

Acute kidney injury (AKI) associated with ICIs has also been reported [4–8], with an estimated incidence between 2% and 30% in ICI-treated patients [9–11]. Even though glomerular diseases have been described [12], the most frequent cause of AKI is acute tubulointerstitial nephritis (ATIN) [8, 13–15]. The pathophysiology of those ICI-induced nephropathies (ICI-AKI) remains unclear, but may involve concomitant treatments [16–20]. Likewise, evidence is scarce regarding the optimal management of ICI-AKI [21].

To suggest potential mechanisms and specific risk factors for ICI-AKI, we conducted a multicentre case–control study, based on reports registered in the French Pharmacovigilance Database (PVD). We aimed to compare the characteristics of patients with ICI-induced nephropathy to the ones of patients diagnosed with other IRAEs.

## MATERIALS AND METHODS

### Database

The PVD gathers all adverse drug reactions (ADRs) reported spontaneously by healthcare professionals and patients. All reports are analysed by clinical pharmacologists of each regional pharmacovigilance centre. It is mandatory for every healthcare professional to notify all ADRs to the corresponding regional pharmacovigilance centre, particularly if serious and/or unexpected. The PVD respects the anonymity of both patients and notifiers.

The PVD has been approved by the National Data Protection Agency. All our data originate from this database. In accordance with European regulation, this observational study did not need the approval of an Institutional Review Board/Independent Ethics Committee [22]. This research was allowed by the Pharmacovigilance network, which was kept informed.

### Query

The PVD was queried for all ADR reports registered from 1985 (creation of the PVD) up to 23 September 2020 and involving, as 'active ingredients', one or more of the following suspected drugs: atezolizumab, avelumab, cemiplimab, durvalumab, ipilimumab, nivolumab and pembrolizumab.

The queried reports were then divided into two groups depending on the type of ADR. All queried reports mentioning at least one of the following terms were classified in the group 'ICI-AKI': the 'High Group Level Term' (HLGT) 'nephropathies' or the HGLT 'renal disorders' or the HLT 'renal function analyses', according to MedDRA (version 22.1) [23]. All queried reports mentioning an effect belonging to any other MedDRA term (to the exclusion of the three abovementioned) were classified in the group 'extrarenal IRAEs'.

For each report, whenever available, data were gathered about the patient [age, sex, body mass index (BMI) and comorbidities], the ICI (therapeutic indication, dosage, date of introduction and of last course of treatment), concomitant drugs and the main features of the ADR (description, notified MedDRA terms, time to onset and outcome). Preexisting chronic kidney disease (CKD), as well as ICI-AKI, were assessed according to the data included in the PVD report (KDIGO classification, estimated glomerular filtration rate, medical history or creatinemia). Notified IRAEs were classified according to MedDRA System Organ Class. We focused on concomitant drugs known for their propensity to induce ATIN: non-steroidal anti-inflammatory drugs (NSAIDs), calcium channel blockers, thiazide and loop diuretics, proton-pump inhibitors (PPIs), hypouricemic drugs, H2 antagonists and fludionone.

### Screening of reports

All reports of 'ICI-AKI' were reviewed by nephrologists and clinical pharmacologists trained in pharmacovigilance to assess their relevance. To increase specificity, cases were not included if AKI could not be directly attributed to the ICI in view of the available data (i.e. prerenal AKI following ICI-induced diarrhea) or when reports were not assessable because of missing data (especially when data on concomitant drugs were not available).

A sample of reports from the 'extrarenal IRAEs' group was randomly included, following a 4:1 ratio of four 'extrarenal IRAEs' for one 'ICI-AKI'. This 4:1 ratio was intended to increase

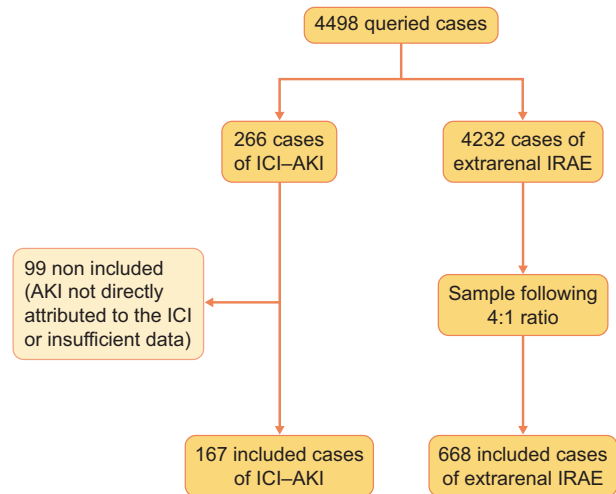


FIGURE 1: Flowchart. AKI: acute kidney injury; ICI-AKI: patients with renal IRAEs; IRAE: immune-related adverse events.

statistical confidence. It is usually not worth going beyond a ratio of four or five controls to one case in case-control studies [24].

When a single patient is subject to several successive distinct reports, this is usually mentioned as a 'related case' in the PVD, and therefore linked to previous reports. This tool was used to seek for potential duplicates.

### Analysis

Descriptive statistics were expressed as mean  $\pm$  standard deviation or as median [interquartile range (IQR)] whenever appropriate. Percentages were calculated for qualitative data. The patients' characteristics were compared with Pearson's Chi-Squared test (with Yates's correction) for categorical variables or the Fisher exact test when the expected number of observations was  $<5$ . Student's *t*-test was used for continuous variables. All variables showing an association with a  $P < 0.05$  were included as covariates in a multivariate analysis, along with sex and BMI. Multivariate analysis was conducted in R [25]. Logistic regressions, with renal injury as an outcome, were run over 40 multiple imputed datasets, using the 'mice' package to impute missing values. Results of the multivariate analysis were expressed as adjusted odds ratios (OR) with their 95% confidence intervals (95% CI), and  $P < 0.05$  was considered statistically significant.

## RESULTS

### Included reports

The query of all specified ADR reports (involving one or more of the ICI and reported between 1985 and 23 September 2020) yielded 4498 reports (Figure 1), 266 (5.9%) of which were classified as ICI-AKI and 4232 (94.1%) as extrarenal IRAEs. After screening this comprehensive list of reports, 99 reports of ICI-AKI were not included because of either insufficient data (especially regarding concomitant drugs) or because AKI could not be directly attributed to the ICI after review, thus 167 reports of ICI-AKI were included (3.7% of the 4498 reports). Among extrarenal IRAEs, 668 reports were sampled to comply with the 4:1 ratio. Among the

Table 1. Patients' characteristics at baseline

Characteristics	ICI-AKI N = 167 (%)	Extrarenal IRAEs N = 668 (%)	P-value
Sex			0.5807
Male	107 (64.1)	410 (61.4)	
Female	60 (35.9)	258 (38.6)	
Age at notification, years	69.1 ± 11.3	64.6 ± 13.1	<0.0001
BMI	24.5 ± 4.3	24.7 ± 5.1	0.7121
Comorbidities			
Chronic kidney disease	20 (12.0)	22 (3.3)	<0.0001
Hypertension	58 (34.7)	156 (23.4)	<b>0.0036</b>
Heart failure	3 (1.8)	4 (0.6)	0.1472
Coronaropathy	8 (4.5)	14 (2.1)	0.0940
Diabetes	15 (9.0)	58 (8.7)	0.9999
Peripheral vascular disease	9 (5.4)	18 (2.7)	0.1295
COPD	17 (10.2)	42 (6.3)	0.1126
Tobacco use	22 (13.2)	95 (14.2)	0.8225
Malignancy			
Lung cancer	67 (40.1)	263 (39.4)	0.9295
Melanoma	50 (29.9)	245 (36.7)	0.1239
Renal cancer	14 (8.4)	27 (4.0)	<b>0.0338</b>
Urothelial cancer	6 (3.6)	9 (1.3)	0.0934
Hodgkin lymphoma	2 (1.2)	6 (0.9)	0.6638
Other	28 (16.8)	118 (17.7)	0.8733
Immunotherapy <sup>a</sup>			
Nivolumab	96 (57.5)	361 (54.9)	0.4761
Pembrolizumab	50 (29.9)	213 (31.9)	0.6957
Ipilimumab	18 (10.8)	101 (15.1)	0.8527
Atezolizumab	7 (4.2)	21 (3.1)	0.6654
Durvalumab	4 (2.4)	16 (2.4)	1
Avelumab	1 (0.6)	5 (0.7)	0.7990
Cemiplimab	1 (0.6)	3 (0.4)	1
Nivolumab ± ipilimumab	8 (4.8)	49 (7.3)	0.3198
Pembrolizumab ± ipilimumab	2 (1.2)	2 (0.3)	0.1804
Nivolumab ± pembrolizumab	0	1 (0.1)	1
Concomitant drugs			
NSAIDs	6 (3.6)	9 (1.3)	0.1034
Calcium channel blocker	23 (13.8)	39 (5.8)	<b>0.0009</b>
Thiazide diuretic	14 (8.4)	24 (3.6)	<b>0.0143</b>
Loop diuretic	15 (9.0)	24 (3.6)	<b>0.0060</b>
PPI	52 (31.1)	94 (14.1)	<0.0001
Hypouricemic	8 (4.8)	11 (1.6)	<b>0.0318</b>
H2 antagonist	1 (0.6)	0	0.2000
Fluindione	11 (6.6)	6 (0.9)	<0.0001

Mean ± standard deviation for continuous variables; COPD: chronic obstructive pulmonary disease; thiazide diuretic: includes hydrochlorothiazide and indapamide.

<sup>a</sup>Patients with combined immunotherapy are also counted in each single immunotherapy's category.

Bold values are p-values of significant results ( $P < 0.05$ ).

sample of extrarenal IRAEs, no report was identified as a 'related case' linked to a report of ICI-AKI for the same patient and vice versa.

### Patients' baseline characteristics

Baseline characteristics of patients with ICI-AKI ( $N = 167$ ) and controls with extrarenal IRAEs ( $N = 668$ ) are detailed in Table 1. Most patients in both groups were male: 107 (64.1%, sex ratio: 1.8) and 410 (61.4%, sex ratio: 1.6), respectively. Patients with ICI-AKI were older (mean age: 69.1 years) than those in the control group (64.6 years). This difference was statistically significant in the univariate analysis ( $P < 0.0001$ ) and confirmed in the multivariate analysis (OR 1.02, 95% CI 1.00–1.04;  $P = 0.0135$ , Table 2). Mean BMI was not significantly different between the two groups.

CKD was significantly more prevalent in patients with ICI-AKI (12.0% versus 3.3%) in the univariate analysis ( $P < 0.0001$ ). This result was confirmed in the multivariate analysis (OR 2.50, 95% CI 1.22–5.14;  $P = 0.0125$ ). Hypertension was significantly more frequent in patients with ICI-AKI (34.7% versus 23.4%) in univariate analysis, but did not stand out in the multivariate analysis ( $P = 0.9451$ ). Other comorbidities were not significantly associated with the occurrence of ICI-AKI.

### Malignancies and ICIs

The most frequent malignancies at the origin of treatment were lung cancer (40.1% among ICI-AKI patients and 39.4% among patients with extrarenal IRAEs) and melanoma (29.9% and 36.7%, respectively) in both groups. Renal cancer was significantly more

Table 2. Multivariate analysis

Characteristics	Odds ratio (95% confidence interval)	P-value
Male	1.05 (0.72–1.53)	0.8073
Age at notification, years	1.02 (1.00–1.04)	<b>0.0135</b>
BMI	0.75 (0.26–2.18)	0.5951
Chronic kidney disease	2.50 (1.22–5.14)	<b>0.0125</b>
Hypertension	1.02 (0.66–1.56)	0.9451
Renal cancer	1.42 (0.67–3.00)	0.3610
Concomitant drugs		
NSAIDs	3.18 (1.07–9.4)	<b>0.0368</b>
Thiazide diuretic	1.56 (0.77–3.19)	0.2192
Loop diuretic	1.37 (0.65–2.89)	0.4052
PPI	2.18 (1.42–3.34)	<b>0.0004</b>
Hypouricemic	1.81 (0.66–4.99)	0.2489
Fluindione	6.53 (2.21–19.31)	<b>0.0007</b>

Thiazide diuretic includes hydrochlorothiazide and indapamide. Bold values are p-values of significant results ( $P < 0.05$ ).

frequent in patients with ICI-AKI in the univariate analysis (8.4% versus 4.0%;  $P = 0.0338$ ) but not in the multivariate analysis ( $P = 0.3610$ ). Other malignancies were not significantly associated with the occurrence of ICI-AKI.

More than half of the patients were treated with nivolumab in each group (Table 1): 57.5% in ICI-AKI patients and 54.9% in patients with extrarenal-IRAEs. Among patients with ICI-AKI, 10 (6.0%) were treated with two concomitant ICIs. In patients with extrarenal IRAEs, 52 (7.8%) were treated with two concomitant ICIs. The relative share of the different ICIs was not significantly different between the two groups.

### Immune-related adverse events

Time to onset for ICI-AKI could be assessed in 136 of the 167 reports, with a median of 83 days (IQR 31–168). Among 167 ICI-AKI reports, 74 (44.3%) mentioned at least one concomitant extrarenal IRAE, mostly haematologic (12, 7.2%), hepatobiliary (11, 6.6%) and/or cutaneous (10, 6.0%) (Table 3).

In the extrarenal IRAEs group, 301 (45.1%) reports mentioned IRAEs belonging to at least two different organs. The most frequent (non-mutually exclusive) IRAEs were cutaneous (131, 19.6%), endocrine (105, 15.7%), respiratory (98, 14.7%) and/or gastrointestinal (97, 14.5%) (Table 3).

### Concomitant drugs

In the multivariate analysis, patients with ICI-AKI were significantly more likely to be treated with fluindione (OR 6.53, 95% CI 2.21–19.31;  $P = 0.0007$ ), an NSAID (OR 3.18, 95% CI 1.07–9.4;  $P = 0.0368$ ) or a PPI (OR 2.18, 95% CI 1.42–3.34;  $P = 0.0004$ ) (Table 2). Among patients with ICI-AKI, five (3.0%) were treated with both fluindione and a PPI, two (1.2%) were treated with both an NSAID and a PPI, and none was treated with both fluindione and a NSAID. In the univariate analysis, patients with ICI-AKI were significantly more likely to be cotreated by a thiazide diuretic, a loop diuretic or a hypouricemic agent (Table 1). However, this association did not remain significant in the multivariate analysis (Table 2).

## DISCUSSION

In this multicentre pharmacovigilance case-control study of 167 patients with ICI-AKI, we shed some light on the specific fea-

tures associated and possibly concurring to ICI-AKI, compared with reports of extrarenal IRAEs as controls.

Most patients (60–65%) were male in both groups, as found in previous studies [17, 26, 27]. This result may seem surprising, as females are generally more prone to autoimmune diseases than males. Nonetheless, it may merely reflect the epidemiology of cancer [28], as no significant sex-associated differences have been described for IRAEs [27].

We found an independent association between the occurrence of ICI-AKI and age or preexisting CKD. Lower baseline renal function has already been retrospectively reported as a risk factor for ICI-AKI [17], while the association between age and ICI-AKI is, to our knowledge, unprecedented [29]. The increased risk of ICI-AKI in elderly seems rational, since age may reflect increased renal frailty in older patients.

Renal cancer was more frequent in ICI-AKI patients in univariate analysis. However, this result did not stand out in the multivariate analysis. This result might have been subject to a confusion bias. Should it be confirmed by further studies, this finding could also be underpinned by the two-way association between CKD and renal cancer [30]. Renal cancer might also foster immune tolerance loss against kidney antigen, but we are unable to draw definite conclusions as it stands.

The median time to onset (around 2 months) dovetails with the available literature on ICI-AKI [9, 11, 15]. On another note, we confirm the high proportion of patients with concomitant IRAEs affecting more than one organ in nearly half of the reports (in both groups). The literature suggests that concomitant extrarenal IRAE may lower the likelihood of renal recovery. Conversely, concomitant treatment with a drug known to cause ATIN may improve renal prognosis [17].

Regarding concomitant drugs, we confirm an independent association between concomitant treatment with a PPI or an NSAID and the occurrence of ICI-AKI [17, 19, 31]. In addition, we report for the first time an independent association between long-term treatment with the vitamin-K antagonist fluindione and ICI-AKI. This finding seems relevant, given that fluindione bears a definite immuno-allergic risk (including ATIN) [32, 33].

There is growing evidence that ICIs may sometimes precipitate (rather than directly induce) ATIN caused by another concomitant nephritogenic treatment such as a PPI, an NSAID, an antibiotic or fluindione [14, 20]. This loss of tolerance to a concomitant treatment may be explained by the activation of latent drug-specific T cells. Other (not mutually exclusive) mechanistic hypotheses for ICI-AKI include recognition by the T-cell of an off-target kidney antigen after immune checkpoint blockade or the formation of auto-antibodies directed against kidney tissue [14, 16, 20].

This multicentre case-control study relies on a large cohort of patients, with a 4:1 ratio and a multivariate analysis to mitigate the impact of potential confounders. The control group included patients with extrarenal IRAEs only, thus helping to approach the specific risk factors for ICI-AKI rather than the risk factors for IRAEs broadly speaking. However, it is limited by classical flaws inherent to pharmacovigilance studies, such as lack of data and under-notification. We did not include reports when concomitant drugs were not available to try to minimize the notification bias, whereby physicians reporting ICI-AKI are more prone to list the concomitant medications. However, this approach led us to rule out a substantial number of reports from the analysis. The heterogeneity of data prevented us from relying on established classifications such as KDIGO [34] and from precisely tracking the timing of sequential IRAEs. Besides, this case-control study cannot pretend to draw definite conclusions

Table 3. Repartition of reported IRAEs

System organ class	ICI-AKI N = 167 (%)	Extrarenal IRAEs N = 668 (%)
>1 concomitant SOC reported	74 (44.3)	301 (45.1)
Blood and lymphatic system disorders	12 (7.2)	46 (6.9)
Cardiac disorders	4 (2.4)	44 (6.6)
Endocrine disorders	6 (3.6)	105 (15.7)
Eye disorders	1 (0.6)	29 (4.3)
Gastrointestinal disorders	5 (3.0)	97 (14.5)
Hepatobiliary disorders	11 (6.6)	80 (12.0)
Immune system disorders	0	16 (2.4)
Infections and infestations	2 (1.2)	21 (3.1)
Metabolism and nutrition disorders	9 (5.4)	38 (5.7)
Musculoskeletal and connective tissue disorders	3 (1.8)	58 (8.7)
Nervous system disorders	5 (3.0)	46 (6.9)
Psychiatric disorders	0	7 (1.0)
Renal and urinary disorders	167 (100)	0
Respiratory, thoracic and mediastinal disorders	9 (5.4)	98 (14.7)
Skin and subcutaneous tissue disorders	10 (6.0)	131 (19.6)
Vascular disorders	2 (1.2)	16 (2.4)

IRAEs are classified depending on their system organ class (SOC; MedDRA) and are not mutually exclusive as some patients experienced several concomitant IRAEs (>1 concomitant SOC reported).

regarding the causal relationship between the studied characteristics and the occurrence of ICI-AKI. Moreover, we may have lacked the power to identify a significant association between some concomitant treatments and ICI-AKI.

This case-control study highlights potential risk factors for ICI-AKI, with a special focus on the role of co-treatments known to cause immuno-allergic ATIN, such as PPIs, NSAIDs and flunidione. ICIs may be a 'second hit' that precipitates AKI caused by another concomitant drug. Further causal confirmation of this pathophysiological hypothesis is awaited. Meanwhile, clinicians should be aware to minimize exposure to co-treatments at risk in patients treated with ICIs.

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## AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by A.O.G., S.B. and N.P. The first draft of the manuscript was written by A.O.G., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## CONFLICT OF INTEREST STATEMENT

The authors do not declare any conflict of interest relevant to the content of this article. The results presented in this paper have not been published previously in whole or in part.

## DATA AVAILABILITY STATEMENT

The French Pharmacovigilance Database (PVD) has been approved by the National Data Protection Agency. All our data originate from this database. In accordance with European regulation, this retrospective observational study of anonymous reports did not need the approval of an Institutional Review Board/Independent Ethics Committee. This research was allowed by the Pharmacovigilance network, which was kept informed.

(See related article by Belliere and Sprangers. 'Prevention is better than cure': warning for comedication in patients receiving immune checkpoint inhibitors to avoid acute kidney injury. *Clin Kidney J* (2022) 15: 1803–1806.)

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