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Review Article

The differentiation and intervention strategies for acute kidney injury after or induced by immune checkpoint inhibitors

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Abstract: With the increasing popularity of immune checkpoint inhibitors (ICIs) in tumor treatment, the incidence of immune-related adverse events (irAEs), including acute kidney injury (AKI), is on the rise. Renal biopsy serves as the gold standard for determining the true etiology of AKI following ICIs administration; however, due to potential risks and associated losses with this procedure, comprehensive analysis of physiological data and predictive models are gradually being incorporated into clinical practice to differentiate AKI etiologies. These include criteria such as a ≥ 100% increase in serum creatinine (Scr) from baseline or a 50% increase accompanied by other pathological manifestations, renal replacement therapy (RRT), or absence of any other reasonable cause. Currently, cessation of ICIs and steroid therapy represent commonly employed treatment approaches; nevertheless, these strategies have inherent side effects and may not be feasible for certain patient populations, such as those with diabetes, posing challenges for clinicians. Recent studies have demonstrated that rituximab, mycophenolate mofetil (MMF), and infliximab can potentially replace steroid therapy in managing ICIs-induced AKI (ICIs-AKI), offering a novel therapeutic perspective. This review provides an overview of non-invasive methods for distinguishing between AKI following ICIs use and ICIs-AKI while discussing strategies for treating ICIs-AKI.

Keywords: Immune checkpoint inhibitors, acute kidney injury, differentiation, treatment

Introduction

Immune checkpoint inhibitors (ICIs) elicit antitumor immune responses by hyperactivating the immune system, ushering in a new era of cancer treatment [1]. However, alongside significantly improving cancer patient survival rates, ICIs are also accompanied by notable adverse effects known as immune-related adverse events (irAEs) [2]. These irAEs can affect various organs, including the kidney [3]. Currently, there is an increasing number of studies focusing on acute kidney injury (AKI) following ICIs administration. The key distinction among these studies lies in whether they differentiate the direct cause of AKI. To facilitate differentiation, we refer to all-cause AKI occurring after ICIs usage as aAKI, while AKI induced by ICIs confirmed by biopsy or other methods are called ICIs-AKI. This distinction between aAKI and ICIs-AKI is crucial due to their different mechanisms and intervention strategies [4]. Therefore, this article primarily aims to summarize methods for distinguishing ICIs-AKI from other forms of AKI and discuss its corresponding treatments.

Clinical features

The incidence of aAKI is primarily around 12.0% [2, 5-9], and the median time from ICIs initiation to AKI is approximately 80 days. When the etiology is limited to ICIs induction, the incidence significantly decreases to only 1.4-5.3% [2, 3, 9-11]. Meanwhile, the median time from the initiation of ICIs to ICIs-AKI typically ranges between 91 and 112 days [7, 11-13]. Interestingly, different types of ICIs can affect the time of onset, one report showed that CTLA-4 inhibitors can start as early as 6-12 weeks after initiation, while PD-1 inhibitors may take 3-6 months [8]. Furthermore, acute interstitial

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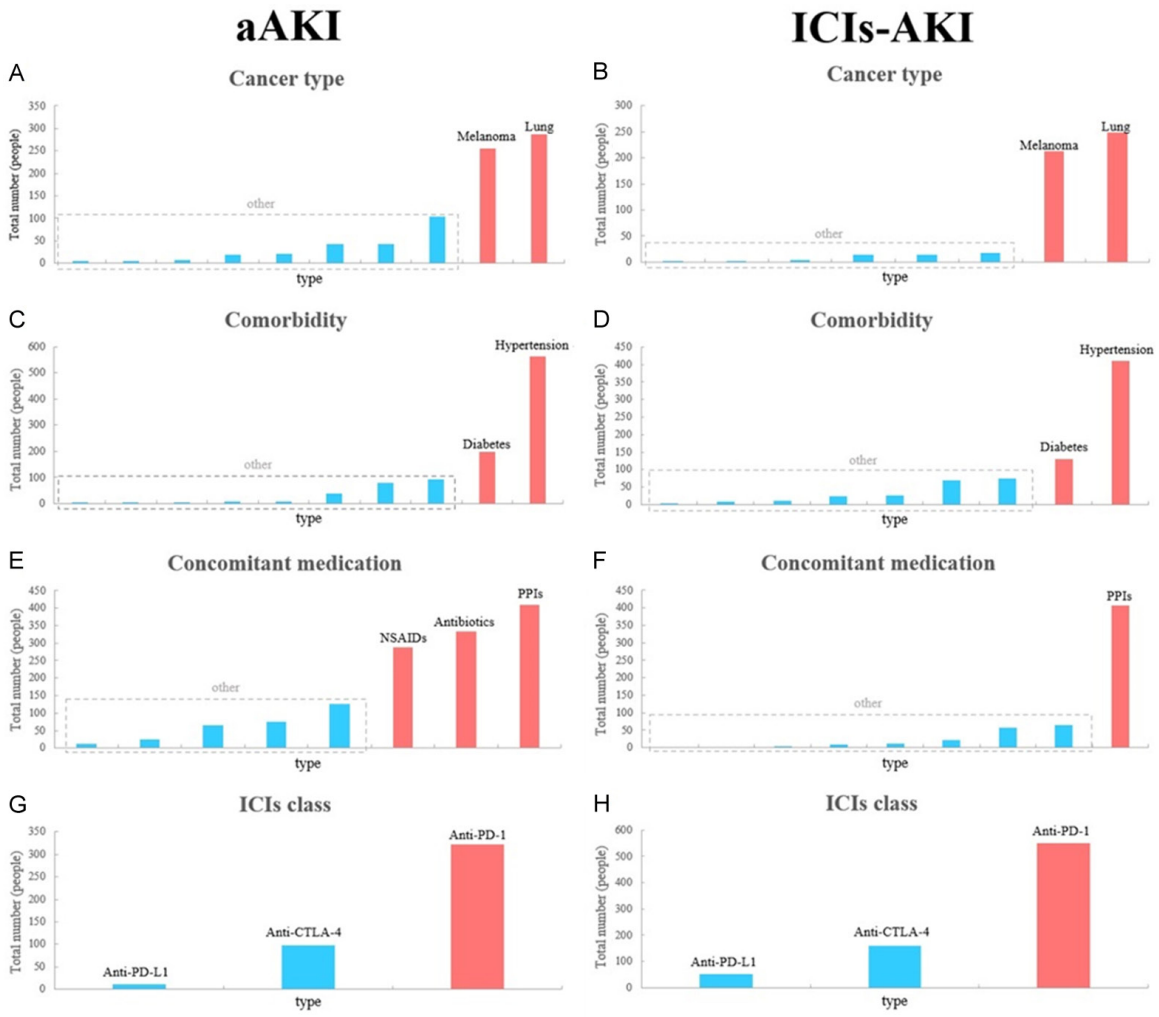

Figure 1. Baseline characteristics of the aAKI and ICIs-AKI. The other types in (A) in ascending order are: glioblastoma multiforme, liquid, colorectum, head and neck, gastroduodenum, breast, hepatobiliary, urinary tract. The other types in (B) in ascending order are: pancreatic, Hodgkin's lymphoma, colorectum, gastrointestinal tract, renal, hepatobiliary. The other types in (C) in ascending order are: congestive hearts failure, chronic obstructive pulmonary disease, autoimmune disease, cerebrovascular disease, coronary heart disease, liver disease, chronic kidney disease, anemia. The other types in (D) in ascending order are: cerebrovascular disease, peripheral vascular disease, coronary heart disease, heart failure, liver disease, chronic obstructive pulmonary disease, chronic kidney disease. The other types in (E) in ascending order are: Allopurinol, steroid, H2 blockers, diuretics, ACEi/ARBs. The other types in (F) in ascending order are: H2 antagonist, ACEi/ARBs, corticosteroids, antibiotics, Fluindione, calcium channel blocker, diuretics, NSAIDs. The types in (G) in ascending order are: anti-PD-L1, anti-CTLA-4, anti-PD-1. The types in (H) in ascending order are: anti-PD-L1, anti-CTLA-4, anti-PD-1. Abbreviations: aAKI, all-cause acute kidney injury that occurs after using immune checkpoint inhibitors; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CTLA-4, cytotoxic T lymphocyte antigen-4; ICIs-AKI, acute kidney injury induced by immune checkpoint inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand; PPIs, proton pump inhibitors.

nephritis (AIN) has been proven to be the most common lesion seen in histopathologic series [11, 13]. However, with the increasing popularity of ICIs, pathological manifestations other than AIN are gradually emerging, distal renal tubular acidosis (RTA), renal granulomatous arteritis, anti-glomerular basement membrane disease (anti-GBM) glomerulonephritis have been reported [14-16]. Sub-nephrotic proteinuria and pyuria are common pathological manifestations of ICIs-AKI [13].

Besides, we have summarized the articles that clearly listed the characteristics of AKI in recent years [2, 4-7, 9, 11-13, 17], as shown in **Figure 1** and **Table 1**. We can see that the

Table 1. Baseline characteristics of the aAKI and ICIs-AKI

Category	aAKI			ICIs-AKI			
Article	Alejandro Meraz-Muño [5]	Marije S. Koks [6]	Megan L. Baker [4]	Shruti Gupta [12]	Cortazar FB [13]	Xiang Yu [7]	Alexandre O. Gérard [17]
Age, median (IQR)	63.0 (55.0 to 68.0)	64.0 (53.0-73.0)	65.4 (57.3, 73.3)	68.0 (59.0-75.0)	67.0 (58.0-74.0)	57.0 (49.0-64.3)	69.1 ± 11.3
Male (%)	70.6	57.3	54.5	62.0	60.0	63.2	64.1
Baseline Scr mg/dL, median (IQR)	0.8 (0.7 to 1.0)	-	0.8 (0.7, 1.0)	1.0 (0.8-1.2)	0.9 (0.8-1.2)	60.5 (50.6, 76.4)	-
Baseline eGFR mL/min/1.73 m^2, median (IQR)	90.0 (72.0 to 99.0)	92.0 (73.0 to 103.0)	86.3 (65.5, 99.3)	73.0 (57.0-90.0)	72.0 (55.0-89.0) (ml/min)	103.6 (89.1, 111.5)	-

Abbreviations: aAKI, all-cause acute kidney injury that occurs after using immune checkpoint inhibitors; eGFR, estimated glomerular filtration rate; ICIs-AKI, induced acute kidney injury by immune checkpoint inhibitors; Scr, serum creatinine.

Risk factor		aAKI	ICIs-AKI
Concomitant medication	PPIs	√	√
	NSAIDs	√	√
	antibiotics	√	√
	diuretics	√	√
	fluindione	√	√
	ACEIs/ARBs	√	
	corticosteroid	√	
	RAF/MEK inhibitors	√	
Comorbidity	CKD	√	√
	hypertension	√	
	cerebrovascular disease	√	
	anemia	√	
	diabetes mellitus	√	
	COVID-19		√
Cancer type	gynecologic cancer	√	
	genitourinary cancer	√	
	renal cell carcinoma		√
	urothelial carcinoma		√
ICIs therapy	ICIs combinations	√	√
	monotherapy with ipilimumab	√	
	PD-1 inhibitors		√
	CTLA-4 inhibitors		√
demography	older	√	√
	male	√	
other	extrarenal irAEs	√	√
	baseline Alb < 30 g/L	√	
	lower baseline eGF		√

Figure 2. Risk factors of aAKI and ICIs-AKI. Abbreviations: aAKI, all-cause acute kidney injury that occurs after using immune checkpoint inhibitors; ACEIs, angiotensin converting enzyme inhibitors; Alb, albumin; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICIs-AKI, acute kidney injury induced by immune checkpoints inhibitors; irAEs, immune related adverse events; NSAIDs, nonsteroidal anti-inflammatory drugs; PD-1, programmed cell death 1; PPIs, proton pump inhibitors.

demography of aAKI and ICIs-AKI are roughly the same: (1) Most common in lung cancer and melanoma; (2) Patients are often complicated with hypertension and diabetes; (3) PD-1 inhibitors are the most commonly used ICIs drugs; (4) Slightly different among concomitant drugs: proton pump inhibitors (PPIs), antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs) are all common in aAKI, while in ICIs-AKI, PPIs are significantly higher than other drugs; (5) Most patients are male; (6) The age is concentrated in 50-70 years old.

Risk factors

Figure 2 lists factors that have been proven to be risk factors of aAKI and ICIs-AKI in recent years. The concomitant medication is the most important issue for us to pay attention to, among which NSAIDs and PPIs have been proven as risk factors in multiple studies, regardless of whether the etiology is limited to ICIs-induced cases [5-7, 9, 12, 13, 17-20], which may be attributed to the nephrotoxicity of these drugs. And for ICIs-AKI, esomeprazole and lansoprazole are the highest risk in PPIs [21]. However, not all drugs with nephrotoxicity combined with ICIs will increase the risk of AKI. In an experiment studying the treatment of non-squamous non-small cell lung cancer (NSCLC), there was no significant difference in the incidence, severity, treatment and renal recovery of AKI between the combination of pembro-

lizumab-carboplatin-pemetrexed group and pembrolizumab monotherapy [22].

Comorbidity is the second largest risk factor, especially chronic kidney disease (CKD) [4, 5, 18, 23]. However, we need to note that CKD patients already have renal dysfunction, making it difficult to determine the true cause of the increased incidence of ICIs-AKI, and there are already articles proving that CKD is not a risk factor [13, 23]. Therefore, CKD patients may not need to stop ICIs, especially when treatment options are limited. Besides, there have been articles reporting that coronavirus disease 2019 (COVID-19) increases the risk of ICIs-AKI, which may be because the pro-inflammatory environment caused by viral infection and the use of ICIs can cause the renal parenchyma to lose its self-tolerance [24, 25]. Meanwhile, in ICIs therapy, nivolumab and ipilimumab were shown to have the greatest risk for ICIs-AKI [7, 11].

Mechanism

AKI caused by non-ICIs can be attributed to various factors, including urinary tract obstruction and hemodynamic AKI/ATN. The precise mechanisms underlying ICIs-AKI remain unknown; however, the following outlines the most probable mechanisms (**Figure 3**).

Loss of tolerance versus self-antigen

T cells are more susceptible to losing tolerance towards native kidney antigens in the presence of ICIs, thereby activating self-reactive B cells and generating autoantibodies against specific self-antigens within organs like the kidney (**Figure 3A**) [1]. Although the exact antigen is currently unidentified, it is likely expressed by tubular cells based on the predominant finding of ATIN on biopsy [3].

Off-target effect

The interaction between PD-L1 on renal tubular epithelial cells and PD-1 on T cells plays a protective role against immune-mediated renal interstitial injury caused by T cell-mediated autoimmunity. However, ICIs can block this pathway, leading to renal injury (**Figure 3B**) [26, 27].

Pro-inflammatory environment

ICIs have the potential to enhance effector T cell migration and activation within renal tissue, while promoting immune cell infiltration and pro-inflammatory cytokine release. Inflammatory mediators such as CXCL-10, TNF-α and IL-6 contribute to an inflammatory microenvironment that ultimately leads to kidney injury (**Figure 3C**) [28, 29].

Re-activation of drug-specific T cells

T cells that were previously primed during exposure to nephritogenic drugs, such as PPIs and NSAIDs, can become latent over time. However, the use of ICIs can reactivate these T cells, leading to the loss of tolerance (**Figure 3D**) [30]. This reactivation may explain the long incubation period observed in ICIs-AKI. Furthermore, this pathway might be associated with the influx of vascular T cells and subsequent development of granuloma formation, potentially explaining the pathophysiology of renal granulomatous arteritis related to CTLA-4 blockade [15].

ICIs bind with kidney-associated cells to form the antigen

Additionally, certain tissues express checkpoint receptors naturally; therefore, when ICIs bind to kidney-associated cells and are recognized as antigens, an immune response is triggered, resulting in the generation or reactivation of T cells against renal tissues (**Figure 3E**) [31].

Moreover, PD-1's inhibition of regulatory cells (Tregs), the interaction between PD-L1 and complement system activation, and the interaction between dendritic cells and T cells in ICIs-AKI along with subsequent activation of T cells may also contribute to this pathophysiological process [28, 32, 33], although further research is warranted due to the limited evidence available.

Prognosis

Given the relatively low incidence rate of ICIs-AKI and the limited articles directly attributing AKI solely to ICIs usage in the literature reviewed so far; our discussion primarily focuses on the consequences associated with aAKI.

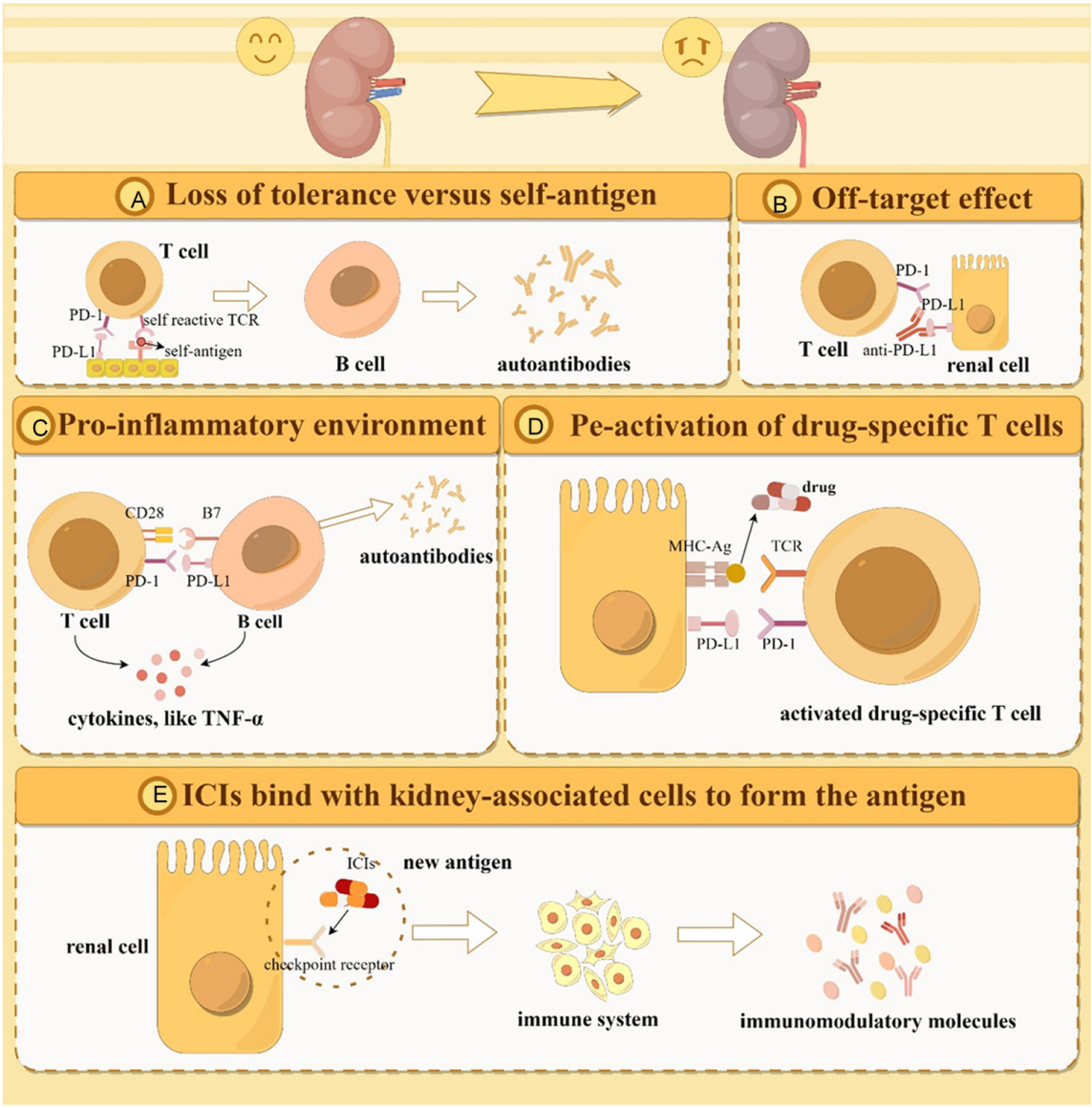

Figure 3. By Figdraw. Mechanisms of ICIs-AKI. A: T cells recognize self-antigens and stimulate B cells to produce antibodies that target tissues; B: The protection pathways of PD-L1 and PD1 are blocked; C: ICIs induce T cells to produce inflammatory factors and break tissues; D: T cells previously exposed to nephrotoxic drugs were reactivated by ICIs; E: The binding of ICIs to kidney tissue results in the formation of antigens. Abbreviations: aAKI, all-cause acute kidney injury that occurs after using immune checkpoint inhibitors; ACEIs, angiotensin converting enzyme inhibitors; Alb, albumin; ARBs, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ICIs-AKI, acute kidney induced by immune checkpoints inhibitors; irAEs, immune related adverse events; NSAIDs, nonsteroidal anti-inflammatory drugs; PD-1, programmed cell death 1; PPIs, proton pump inhibitors.

The effect of AKI on mortality rates remains uncertain [4, 5, 34]; however, non-recovery from AKI has been identified as an independent predictor for increased mortality risk [4]. Ming-Su Ji et al. found that patients who failed to recover renal function within 90 days after onset had a higher risk of death compared to those who did recover their renal function [9]. These findings align with another study that reported an increased mortality risk among patients with persistent kidney dysfunction (non-recovery) [34].

Differentiation and diagnosis

The incorrect attribution of AKI etiology to ICIs not only results in improper treatment but also exacerbates cancer conditions due to the sus-

Table 2. The way of differentiating ICIs-AKI from aAKI

Article	Method
Shruti Gupta [12]	Patients were eligible for inclusion if they had acute kidney injury (AKI) that was directly attributed to the immune checkpoint inhibitors (ICIs) by the treating provider and if they met either of the following criteria: (1) an increase in serum creatinine (Scr) ≥ 100% from baseline or treatment with renal replacement therapy (RRT); (2) an increase in Scr ≥ 50% from baseline and at least one of the following: ATIN on kidney biopsy; ICIs therapy held for at least once cycle due to concern for induced acute kidney injury by immune checkpoint inhibitors (ICIs-AKI); or treatment with corticosteroids due to concern for ICIs-AKI.
Harish Seethapathy [2]	(1) AKI attributed to ICIs-AKI either by biopsy or subspecialist evaluation; (2) AKI without alternative cause** occurring in the context of concurrent immune related adverse events (irAEs).
Frank B. Cortazar [13]	AKI was attributed directly to the ICIs by the treating provider and the patient had at least a doubling of Scr or the requirement for RRT.
Shruti Gupta [3]	(1) creatinine elevation of ≥ 1.5 times the baseline value on at least two consecutive values or need for RRT; (2) absence of an alternative plausible cause; (3) at least one of three additional criteria: sterile pyuria, eosinophilia, or recent or concomitant non-kidney irAEs.

**Patient did not have sepsis, nephrotoxin exposure, or a hemodynamic cause, and they did not improve with an intravenous fluid challenge. Abbreviations: aAKI, all-cause acute kidney injury that occurs after using immune checkpoint inhibitors; ICIs-AKI, induced acute kidney injury by immune checkpoint inhibitors; irAEs, immune related adverse events; RRT, renal replacement therapy; Scr, serum creatinine.

pension of ICIs therapy. Therefore, it is crucial to differentiate between ICIs-AKI and non-ICIs-AKI before determining the treatment plan. **Table 2** presents several recently adopted methods for this purpose.

Biopsy

When suspecting ICIs-related nephrotoxicity, especially in cases of significant renal function damage with an unknown cause, strong caution should be given. Early administration of corticosteroids (within 3 days after ICIs-AKI) has been shown to increase the likelihood of renal function recovery [12]. Additionally, patients with higher stages of ICIs-AKI have a lower probability of renal recovery. It is important to note that kidney injury in patients treated with ICIs often develops gradually and may not meet the definition of AKI, underscoring the significance of early recognition and treatment of ICIs-AKI to prevent disease deterioration and hinder cancer patient management [12, 35].

Non-invasive methods

While renal biopsy remains the gold standard, its potential harm to patients is difficult to estimate; therefore, other non-invasive methods are more valuable.

Physiological data: As shown in **Table 2**, clinically used indicators include an increase in serum creatinine (Scr) ≥ 100% from baseline, treatment with renal replacement therapy (RRT), and an increase in Scr ≥ 50% from baseline accompanied by other manifestations or the absence of an alternative plausible cause. Studies have also highlighted additional differentiating indicators.

Compared with aAKI, various indicators significantly increase in cases of ICIs-AKI: (1) Cytological analysis: several specific immune cells, including CD4 memory, T helper cells, dendritic cells in the kidney tissue [28], and soluble interleukin-2 receptor (sIL-2R) level [36]; (2) Urinalysis: IL-2, IL-10, TNF-α, and urine retinol binding protein/urine creatinine (uRBP/Cr) [28, 37]; (3) Serology: serum C-reactive protein (CRP) [37]. Recently, a report found that IgG2 is dominant in anti-GBM glomerulonephritis induced by pembrolizumab, while IgG1 or IgG4+ is dominant in classical anti-GBM glomerulonephritis [16]. This suggests that the IgG subclass may be useful in differentiating between ICIs and non-ICIs-AKI. Dysregulation of B and T cells through flow cytometry and the lymphocyte transformation test (LTT) can also be helpful [36, 38].

In cases where histological features are limited to ATIN, compared with non-ICIs related cases, ICIs-AKI presents milder forms of AKI, lower creatinine levels, higher urinary leukocyte counts, longer periods between offending drug initiation and ATIN diagnosis, as well as differences in the occurrence of flare after drug re-exposure [39]. T cells also play a crucial role in discrimination: antigen-independent activated CD8+ T cells, CD163+ macrophages, and CD4+ CD25+ Treg cells have been demonstrated to increase in patients with ICIs-TIN [40]. Additionally, clonotype analysis revealed that the urinary T cell receptors (TCRs) are significantly enriched for a TCR repertoire predominantly found in infiltrating kidney tissue T cells compared to blood TCRs of a patient with ICIs-AIN [41].

Prediction model: With advances in science and technology, obtaining patient information through big data computing has gradually been applied clinically [42]; one study established an ICIs-AKI prediction model based on machine learning algorithms to achieve early prediction of AKI events regardless of the type of ICIs drugs they are receiving (except nivolumab) [7].

Extrarenal irAEs have also shown potential as indicators recently; however, there have been many controversies surrounding this topic, which requires further research [2, 3, 23].

Treatment

When AKI is determined to be induced by ICIs, resolving an irAE may take precedence over the cancer response to ICIs [43]. Particularly in life-threatening situations, consideration should be given to using an antidote such as plasma exchange (to remove circulating ICIs) and abatacept (to induce co-stimulation blockade), which have been validated by several reports [43, 44].

Steroids

Steroids are commonly used traditional drugs for treating ICIs-AKI and their therapeutic efficacy has been confirmed [8, 11, 13]. The following is the most recent discussion on the use of steroids.

Start time: There is no exact definition for the initiation time; however, it is appropriate to commence steroid treatment when AKI severity is high and accompanied by other irAEs. Mark A. Perazella et al. proposed an algorithm: if AKI caused by ICIs is confirmed at stage 2/3 and there are other irAEs along with sterile pyuria and/or white blood cell (WBC) cast present, steroids will be administered; otherwise, steroids will be initiated after the kidney biopsy confirms AIN [45].

Duration: Some articles have reported favorable prognoses in patients receiving longer-term steroid therapy [8, 11]. However, in the study conducted by Shruti Gupta et al., no significant difference was observed in patients treated with shorter (28 days or less) versus longer durations of corticosteroids [46]. Additionally, certain studies have suggested that steroids may potentially hinder the antitumor effect of ICIs [4, 47]. Considering these findings and the associated side effects of steroids, short-term usage appears to be a more rational choice.

Dose: At the initial stage of treatment, the dosage of steroids can be escalated. In Sandhya Manohar et al.'s cohort study, patients who achieved complete recovery of renal function received a higher dose of steroids (2.79 mg/kg per month; range 1.45-3.2) compared to those with partial recovery (1.74 mg/kg per month; range 0.8-3.2). Additionally, among the patients who initially received IV pulse steroids, 5 out of 7 experienced complete restoration of kidney function [48].

The most commonly employed regimen for steroid reduction involves tapering over 4-6 weeks [29, 49]. However, there is an ongoing debate regarding the optimal rate at which to reduce steroid dosage. Meghan D Lee et al.'s findings demonstrated that rapid tapering over a span of 3 weeks resulted in favorable kidney outcomes for patients with ICIs-nephritis [50]. Conversely, some articles suggested caution against excessively swift reductions in steroid dosage [48, 51], as one report indicated that a rapid taper over 4 weeks led to rebound AKI while a slow taper lasting at least 8-12 weeks was better tolerated [48]. Therefore, further research is warranted in this area.

Moreover, immune cell analysis during ICIs treatment may offer valuable insights into guiding management strategies for ICIs-AKI and

determining appropriate immunosuppressive treatments and optimal steroid dosages since extensive T cell activation induced by ICIs can be reversed through steroid administration [28].

Other drugs

While the therapeutic efficacy of steroids is significant, their potential adverse effects cannot be overlooked and should be carefully considered for certain patient populations, such as those with diabetes, where the disadvantages may outweigh the benefits [52]. Meanwhile, discontinuing ICIs treatment is unfavorable for cancer patients as it can result in cancer progression. Recently, several alternatives to steroids, such as rituximab, mycophenolate mofetil (MMF), and infliximab, have been explored in various studies and have shown promising outcomes. Cyclophosphamide has also been mentioned as a potential option [3].

Rituximab: A monoclonal anti-CD20 antibody can be administered without interrupting ICIs treatment. In the study by Sehrish Qureshi et al., it was observed that rituximab enabled patients to continue receiving ICIs while achieving renal and disease remission, without inhibiting the antineoplastic effects of ICIs therapy [53]. Another study by Praveen Ratanasrimetha et al. demonstrated a significant improvement in renal function when rituximab was administered to a patient with metastatic clear cell renal cell carcinoma who developed ICIs-membranous nephropathy [54].

MMF: MMF can serve as an effective frontline therapy for AKI when steroids are contraindicated. Shlomit Jessel et al. reported a case where an AKI patient with diabetes was treated with MMF instead of high-dose steroids due to concerns about blood glucose control and increased morbidity associated with conventional steroid therapy. Within 30 days of initiating MMF treatment, the patient's creatinine level decreased to 1.3 mg/dL, and immunosuppressive therapy was gradually tapered off over a period of 2 months without any recurrence of AIN [52]. Another article reported that among the seven individuals who received MMF, one achieved complete recovery while six experienced partial recovery [13].

Infliximab: Infliximab is a worthy option for steroid-resistant patients. Omar Mamlou et al. observed one case did not respond to steroids but did respond partially to infliximab [30], and another report found no association between infliximab and cancer progression with the exception of genitourinary cancers [55]. These may be due to infliximab's immediate action to block TNF-α caused by ICIs [30].

Lower levels of serum sodium and interstitial fibrosis in kidney tissue, along with a significant decrease in urine T lymphocyte count, can serve as reliable indicators for renal response to treatment [41, 56, 57]. Several articles have investigated factors influencing the recovery of AKI and identified baseline anemia, baseline albumin (Alb) < 30 g/L, use of diuretics, duration, and occurrence of AKI episodes, presence of concomitant extrarenal irAEs, higher baseline eGFR, and lung cancer as independent risk factors for patient mortality [4, 9, 12, 13]. Conversely, higher baseline body mass index (BMI), use of ACEIs/ARBs (angiotensin converting enzyme inhibitors/angiotensin receptor blockers), and chemotherapeutic agents were found to be protective factors against patient mortality [9, 23]. Besides, a study on PD-1 inhibitors for advanced NSCLC revealed that better progression-free survival (PFS) and longer OS were associated with neutrophil/lymphocyte ratio (NLR) < 5, lactate dehydrogenase (LDH) < 240 U/L, or prognostic nutrition index (PNI) ≥ 45 [58]. Furthermore, previous use of ATIN-causing therapies in combination therapy increases the likelihood of renal function recovery [12, 13], which is linked to decreased positive results in drug-induced lymphocyte stimulation tests after discontinuation of medication [59].

Should patients recover from ICIs-AKI rechallenge with ICIs?

ICIs therapy has demonstrated significant therapeutic efficacy across various tumors and plays a crucial role in improving PFS and OS for patients [56]. Although some oncology guidelines recommend permanent discontinuation of ICIs for Grade 3 or 4 AKI [60], numerous studies have shown that most patients with ICIs-AKI can benefit from rechallenge with ICIs.

Alejandro Meraz-Muñoz et al. reported only one case (8.3%) of recurrent AKI, and if limited to ICIs-AKI as the cause, the recurrence rate would be 12.5% [5]. Similar findings from other

researches support this notion and indicate that the incidence of AKI upon rechallenge with ICIs following recovery from ICIs-AKI is not high [3, 11-13]. Moreover, in Mar Riveiro-Barciela et al. report, 85.0% of experts believe that after the complete recovery of renal function, it can be rechallenged [49].

Considering rechallenges in patients who show no evidence of harm when rechallenged with ICIs seems reasonable, particularly when treatment options are limited. Therefore, it is recommended to follow the principle of 'three lows' for arranging ICIs rechallenge, which includes late start, low dosage, and de-escalation approach.

"Late start" refers to the non-emergency rechallenge of ICIs and it is recommended to initiate treatment after the complete recovery of kidney function. According to Cortazar et al., patients who experienced recurrent AKI were rechallenged sooner after the initial AKI episode [13], and it has been established that the benefits on the tumor persist even after discontinuation of ICIs treatment [43]. The term "low dosage" indicates initiating therapy with a low dose of steroids. One study reported that patients recovering from ICIs-AIN can be rechallenged while taking low-dose prednisone (10 mg/d) [48]. The "de-escalation approach" suggests transitioning from combination drug therapy to monotherapy when rechallenging, but PD-L1 inhibitors to CTLA4 inhibitors would not be recommended because of a higher systemic toxicity rate [61]. Additionally, discontinuing other drugs associated with AKI and regularly evaluating immune cells in urine is necessary; an increase in T cell count in urine may indicate a recurrence of ICIs-AKI [41, 50].

Prevention

Firstly, vigilance towards risk factors is crucial. Apart from the aforementioned risk factors, there are methods for predicting high-risk populations. HLA typing assay could be valuable for identifying genetically susceptible or potentially beneficial individuals prior to ICIs treatment [62]. Biomarkers might also play a significant role in diagnostic and therapeutic management. Low NLR, low platelet-to-lymphocyte ratio (PLR), high PNI, elevated expression of neutrophil marker CD177, clonal expansion of CD8 T-cells, and baseline IL-17 levels have been confirmed as predictive markers for irAEs [58, 63, 64].

Secondly, the choice of ICIs therapy should be considered. Durvalumab ± low-dose tremelimumab and avelumab consistently ranked among the top three safest treatments for grade 1-5 or grade 3-5 AKI, according to CTCAE criteria [10]. Besides, given that ICIs-AKI may involve the reactivation of drug-specific T cells, it is advisable to replace nephrotoxic drugs in patients at potential risk of ICIs-AKI [7, 59].

Thirdly, vigilance in monitoring during treatment is crucial. A case reported by Koya Nagase et al. highlighted pembrolizumab-induced immune-related adverse events masked by pemetrexed nephropathy [65], emphasizing the importance of considering single etiology and drug-induced nephrotoxicity to avoid missed diagnosis of AKI during ICIs treatment. Regular urinalysis, renal function assessment, and urography are also recommended throughout ICIs treatment [51].

Conclusion

As ICIs become more widely used in the clinic, clinicians need to fully evaluate the ICIs used by patients to avoid unnecessary injury. Before treatment, methods such as biopsy or a comprehensive analysis of clinical indicators should be employed to differentiate the etiology of AKI. Once ICIs are confirmed as the cause, steroids are the first choice, though the treatment is not yet clear, it is advised that high-severity AKI accompanied by other irAEs warrants early steroid administration with an initial dose escalation and subsequent tapering over a period of 4-6 weeks, and keep the overall treatment duration as short as possible. If steroids are not suitable drugs, rituximab, MMF, and infliximab can also be considered. After recovering from ICIs-AKI, patients should consider rechallenging ICIs, and follow the "three lows" principle.

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Disclosure of conflict of interest

None.

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References

[1] Longhitano E, Muscolino P, Lo Re C, Ferrara SA, Cernaro V, Gembillo G, Tessitore D, Speranza D, Figura F, Santarpia M, Silvestris N, Santoro D and Franchina T. Immune checkpoint inhibitors and the kidney: a focus on diagnosis and management for personalised medicine. Cancers (Basel) 2023; 15: 1891.

[2] Seethapathy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehn I, Cortazar FB, Leaf DE, Mooradian MJ, Villani AC, Sullivan RJ, Reynolds K and Sise ME. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clin J Am Soc Nephrol 2019; 14: 1692-1700.

[3] Gupta S, Cortazar FB, Riella LV and Leaf DE. Immune checkpoint inhibitor nephrotoxicity: update 2020. Kidney360 2020; 1: 130-140.

[4] Baker ML, Yamamoto Y, Perazella MA, Dizman N, Shirali AC, Hafez N, Weinstein J, Simonov M, Testani JM, Kluger HM, Cantley LG, Parikh CR, Wilson FP and Moledina DG. Mortality after acute kidney injury and acute interstitial nephritis in patients prescribed immune checkpoint inhibitor therapy. J Immunother Cancer 2022; 10: e004421.

[5] Meraz-Muñoz A, Amir E, Ng P, Avila-Casado C, Ragobar C, Chan C, Kim J, Wald R and Kitchlu A. Acute kidney injury associated with immune checkpoint inhibitor therapy: incidence, risk factors and outcomes. J Immunother Cancer 2020; 8: e000467.

[6] Koks MS, Ocak G, Suelmann BBM, Hulsbergen-Veelken CAR, Haitjema S, Vianen ME, Verhaar MC, Kaasjager KAH and Khairoun M. Immune checkpoint inhibitor-associated acute kidney injury and mortality: an observational study. PLoS One 2021; 16: e0252978.

[7] Yu X, Wu R, Ji Y, Huang M and Feng Z. Identifying patients at risk of acute kidney injury among patients receiving immune checkpoint inhibitors: a machine learning approach. Diagnostics (Basel) 2022; 12: 3157.

[8] Oleas D, Bolufer M, Agraz I, Felip E, Muñoz E, Gabaldón A, Bury R, Espinel E, Serón D, García-Carro C and Soler MJ. Acute interstitial nephritis associated with immune checkpoint inhibitors: a single-centre experience. Clin Kidney J 2020; 14: 1364-1370.

[9] Ji MS, Wu R, Feng Z, Wang YD, Wang Y, Zhang L, Sun XF, Chen XM, He KL and Cai GY. Incidence, risk factors and prognosis of acute kidney injury in patients treated with immune checkpoint inhibitors: a retrospective study. Sci Rep 2022; 12: 18752.

[10] Liu F, Wang Z, Li X, Zhang Z, Yang Y, Chen J, Chen D, Wu L, Liu X, Han S, Wang F, Wahafu W, Gao Y, Ren S, Xing N, Cai G and Chen X. Comparative risk of acute kidney injury among cancer patients treated with immune checkpoint inhibitors. Cancer Commun (Lond) 2023; 43: 214-224.

[11] Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, Le DT, Lipson EJ, Glezerman IG, Wolchok J, Cornell LD, Feldman P, Stokes MB, Zapata SA, Hodi FS, Ott PA, Yamashita M and Leaf DE. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int 2016; 90: 638-647.

[12] Gupta S, Short SAP, Sise ME, Prosek JM, Madhavan SM, Soler MJ, Ostermann M, Herrmann SM, Abudayyeh A, Anand S, Glezerman I, Motwani SS, Murakami N, Wanchoo R, Ortiz-Melo DI, Rashidi A, Sprangers B, Aggarwal V, Malik AB, Loew S, Carlos CA, Chang WT, Beckerman P, Mithani Z, Shah CV, Renaghan AD, Seigneux S, Campedel L, Kitchlu A, Shin DS, Rangarajan S, Deshpande P, Coppock G, Eijgelsheim M, Seethapathy H, Lee MD, Strohbehn IA, Owen DH, Husain M, Garcia-Carro C, Bermejo S, Lumlertgul N, Seylanova N, Flanders L, Isik B, Mamlouk O, Lin JS, Garcia P, Kaghazchi A, Khanin Y, Kansal SK, Wauters E, Chandra S, Schmidt-Ott KM, Hsu RK, Tio MC, Sarvode Mothi S, Singh H, Schrag D, Jhaveri KD, Reynolds KL, Cortazar FB and Leaf DE; ICPi-AKI Consortium Investigators. Acute kidney injury in patients treated with immune checkpoint inhibitors. J Immunother Cancer 2021; 9: e003467.

[13] Cortazar FB, Kibbelaar ZA, Glezerman IG, Abudayyeh A, Mamlouk O, Motwani SS, Murakami N, Herrmann SM, Manohar S, Shirali AC, Kitchlu A, Shirazian S, Assal A, Vijayan A, Renaghan AD, Ortiz-Melo DI, Rangarajan S, Malik AB, Hogan JJ, Dinh AR, Shin DS, Marrone KA, Mithani Z, Johnson DB, Hosseini A, Uprety D, Sharma S, Gupta S, Reynolds KL, Sise ME and Leaf DE.

Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. J Am Soc Nephrol 2020; 31: 435-446.
[14] Herrmann SM, Alexander MP, Romero MF and Zand L. Renal tubular acidosis and immune checkpoint inhibitor therapy: an immune-related adverse event of PD-1 inhibitor-a report of 3 cases. Kidney Med 2020; 2: 657-662.
[15] Lemoine M, Dilly B, Curie A, Hébert V, Laurent C, Hanoy M, Grangé S, Guerrot D, François A and Bertrand D. Ipilimumab-induced renal granulomatous arteritis: a case report. BMC Nephrol 2019; 20: 366.
[16] El Yamani N, Cote G, Riopel J, Marcoux N, MacWay F, Philibert D and Agharazii M. Pembrolizumab-induced anti-GBM glomerulonephritis: a case report. Kidney Med 2023; 5: 100682.
[17] Gérard AO, Barbosa S, Parassol N, Andreani M, Merino D, Cremoni M, Laurain A, Pinel S, Bourneau-Martin D, Rocher F, Esnault VLM, Borchiellini D, Sicard A and Drici MD; French Network of Pharmacovigilance Centers. Risk factors associated with immune checkpoint inhibitor-induced acute kidney injury compared with other immune-related adverse events: a case-control study. Clin Kidney J 2022; 15: 1881-1887.
[18] Liu C, Wei W, Yang L, Li J, Yi C, Pu Y, Yin T, Na F, Zhang L, Fu P and Zhao Y. Incidence and risk factors of acute kidney injury in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. Front Immunol 2023; 14: 1173952.
[19] Thummalapalli R, Melms JC, Mier J and Izar B. Rapid evolution of acute kidney injury after initial infusion of pembrolizumab in a melanoma patient concurrently treated with RAF/MEK inhibitors. Melanoma Res 2020; 30: 219-222.
[20] Zhao J, Feng Y and Liu GW. Knowledge domains and emerging trends in immune-related adverse events from immune checkpoint inhibitors: a bibliometrics and visualized analysis. Heliyon 2024; 10: e27832.
[21] Kato K, Mizuno T, Koseki T, Ito Y, Hatano M, Takahashi K, Yamada S and Tsuboi N. Concomitant proton pump inhibitors and immune checkpoint inhibitors increase nephritis frequency. In Vivo 2021; 35: 2831-2840.
[22] Gupta S, Strohbehn IA, Wang Q, Hanna PE, Seethapathy R, Prosek JM, Herrmann SM, Abudayyeh A, Malik AB, Loew S, Carlos CA, Chang WT, Beckerman P, Mithani Z, Shah CV, Renaghan AD, de Seigneux S, Campedel L, Kitchlu A, Shin DS, Coppock G, Lumlertgul N, Garcia P, Ortiz-Melo DI, Rashidi A, Sprangers B, Aggarwal V, Benesova K, Jhaveri KD, Cortazar FB, Weins A, Zuo Y, Mooradian MJ, Reynolds KL, Leaf DE, Sise ME, Campedel L, Salem JE, Bagnis CI, Gupta S, Leaf DE, Singh H, Motwani SS, Murakami N, Tio MC, Mothi SS, Selamet U, Weins A, Loew S, Schmidt-Ott KM, Chang W, Jhaveri KD, Wanchoo R, Khanin Y, Hirsch JS, Sakhiya V, Stalbow D, Wu S, Ortiz-Melo DI, Ostermann M, Lumlertgul N, Seylanova N, Cennamo A, Rigg A, Shaunak N, Kibbelaar ZA, Benesova K, Deshpande P, Sise ME, Reynolds KL, Seethapathy HS, Lee M, Strohbhen IA, Mooradian MJ, Hanna PE, Wang Q, Seethapathy R, Herrmann SM, Isik B, Glezerman IG, Cortazar FB, Aggarwal V, Chandra S, Prosek JM, Madhavan SM, Owen DH, Husain M, Beckerman P, Mini S, Anand S, Garcia P, Kaghazchi A, Rangarajan S, Shin DS, Cherry G, Carlos CA, Hsu RK, Kisel A, Rashidi A, Kansal SK, Albert N, Carter K, Donley V, Young T, Cigoi H, De Seigneux S, Koessler T, Sprangers B, Wauters E, Shah CV, Eijgelsheim M, Mithani Z, Pagan JA, Zuo Y, Coppock G, Hogan JJ, Abudayyeh A, Mamlouk O, Lin JS, Page V, Kitchlu A, Short SAP, Renaghan AD, Gaughan EM, Malik AB, Soler MJ, García-Carro C, Bermejo S, Felip E, Muñoz-Couselo E and Carreras MJ. Acute kidney injury in patients receiving pembrolizumab combination therapy versus pembrolizumab monotherapy for advanced lung cancer. Kidney Int 2022; 102: 930-935.
[23] Abdelrahim M, Mamlouk O, Lin H, Lin J, Page V, Abdel-Wahab N, Swan J, Selamet U, Yee C, Diab A, Suki W and Abudayyeh A. Incidence, predictors, and survival impact of acute kidney injury in patients with melanoma treated with immune checkpoint inhibitors: a 10-year single-institution analysis. Oncoimmunology 2021; 10: 1927313.
[24] Buyansky D, Fallaha C, Gougeon F, Pépin MN, Cailhier JF and Beaubien-Souligny W. Acute tubulointerstitial nephritis in a patient on anti-programmed death-ligand 1 triggered by COVID-19: a case report. Can J Kidney Health Dis 2021; 8: 20543581211014745.
[25] Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. Immunotherapy 2020; 12: 269-273.
[26] Nikolopoulos P, Liapis G, Giannakopoulos P, Kotsantis I, Drouzas K and Lionaki S. Rapidly progressive pauci-immune glomerulonephritis with aberrant fibrinoid necrosis associated with atezolizumab, an immune check point inhibitor: a case report and review of literature. Antibodies (Basel) 2023; 12: 10.
[27] Franzin R, Netti GS, Spadaccino F, Porta C, Gesualdo L, Stallone G, Castellano G and Ranieri E. The use of immune checkpoint inhibitors in oncology and the occurrence of AKI: where do we stand? Front Immunol 2020; 11: 574271.
[28] Farooqui N, Zaidi M, Vaughan L, McKee TD, Ahsan E, Pavelko KD, Villasboas JC, Markovic S, Taner T, Leung N, Dong H, Alexander MP and Herrmann SM. Cytokines and immune cell

phenotype in acute kidney injury associated with immune checkpoint inhibitors. Kidney Int Rep 2022; 8: 628-641.
[29] Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, Atkins MB, Brassil KJ, Caterino JM, Chau I, Davies MJ, Ernstoff MS, Fecher L, Ghosh M, Jaiyesimi I, Mammen JS, Naing A, Nastoupil LJ, Phillips T, Porter LD, Reichner CA, Seigel C, Song JM, Spira A, Suarez-Almazor M, Swami U, Thompson JA, Vikas P, Wang Y, Weber JS, Funchain P and Bollin K. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 2021; 39: 4073-4126.
[30] Mamlouk O, Selamet U, Machado S, Abdelrahim M, Glass WF, Tchakarov A, Gaber L, Lahoti A, Workeneh B, Chen S, Lin J, Abdel-Wahab N, Tayar J, Lu H, Suarez-Almazor M, Tannir N, Yee C, Diab A and Abudayyeh A. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. J Immunother Cancer 2019; 7: 2.
[31] Perazella MA and Shirali AC. Nephrotoxicity of cancer immunotherapies: past, present and future. J Am Soc Nephrol 2018; 29: 2039-2052.
[32] Tominaga K, Takeuchi K, Takakuma S, Sakamoto E, Hatanaka S, Kajimoto Y, Toda E, Terasaki Y, Kunugi S, Terasaki M and Shimizu A. Immune checkpoint inhibitors associated granulomatous small vessel vasculitis accompanied with tubulointerstitial nephritis: a case report. BMC Nephrol 2023; 24: 48.
[33] Tampe D, Kopp SB, Baier E, Hakroush S and Tampe B. Compartmentalization of intrarenal programmed cell death protein 1-ligand 1 and its receptor in kidney injury related to immune checkpoint inhibitor nephrotoxicity. Front Med (Lausanne) 2022; 9: 902256.
[34] Kanbay M, Copur S, Siriopol D, Yildiz AB, Berkkan M, Popa R, Hasbal NB, Ortiz A and Perazella MA. The association between acute kidney injury and outcomes in cancer patients receiving immune checkpoint inhibitor therapy: a systematic review and meta-analysis. Clin Kidney J 2022; 16: 817-826.
[35] Verploegen MFA, Boers-Sonderen MJ, Piet B and Wetzels JFM. Kidney injury in patients treated with immune checkpoint inhibitors does not meet KDIGO-AKI criteria. Kidney360 2021; 3: 524-529.
[36] Sise ME, Wang Q, Seethapathy H, Moreno D, Harden D, Smith RN, Rosales IA, Colvin RB, Chute S, Cornell LD, Herrmann SM, Fadden R, Sullivan RJ, Yang NJ, Barmettler S, Wells S, Gupta S, Villani AC, Reynolds KL and Farmer J. Soluble and cell-based markers of immune checkpoint inhibitor-associated nephritis. J Immunother Cancer 2023; 11: e006222.
[37] Isik B, Alexander MP, Manohar S, Vaughan L, Kottschade L, Markovic S, Lieske J, Kukla A, Leung N and Herrmann SM. Biomarkers, clinical features, and rechallenge for immune checkpoint inhibitor renal immune-related adverse events. Kidney Int Rep 2021; 6: 1022-1031.
[38] Moturi K, Sharma H and Hashemi-Sadraei N. Nephrotoxicity in the age of immune checkpoint inhibitors: mechanisms, diagnosis, and management. Int J Mol Sci 2023; 25: 414.
[39] Draibe JB, García-Carro C, Martinez-Valenzuela L, Agraz I, Fulladosa X, Bolufer M, Tango A, Torras J and Soler MJ. Acute tubulointerstitial nephritis induced by checkpoint inhibitors versus classical acute tubulointerstitial nephritis: are they the same disease? Clin Kidney J 2020; 14: 884-890.
[40] Xu LY, Zhao HY, Yu XJ, Wang JW, Zheng XZ, Jiang L, Wang SX, Liu G and Yang L. Clinicopathological features of kidney injury related to immune checkpoint inhibitors: a systematic review. J Clin Med 2023; 12: 1349.
[41] Singh S, Clemente LC, Parra ER, Tchakarov A, Yang C, Li Y, Long JP, Yee C and Lin JS. Urinary T cells are detected in patients with immune checkpoint inhibitor-associated immune nephritis that are clonotypically identical to kidney T cell infiltrates. Oncoimmunology 2022; 11: 2124678.
[42] Yang B, Gou W, Lan N, Shao Q, Hu W, Xue C and Liu N. Tislelizumab induced dual organs dysfunction in a patient with advanced esophageal squamous cell carcinoma: a case report. Front Oncol 2024; 14: 1347896.
[43] Belliere J, Mazieres J, Meyer N, Chebane L and Despas F. Renal complications related to checkpoint inhibitors: diagnostic and therapeutic strategies. Diagnostics (Basel) 2021; 11: 1187.
[44] Laamech R, Terrec F, Emprou C, Toffart AC, Pierret T, Naciri-Bennani H, Rostaing L and Noble J. Efficacy of plasmapheresis in nivolumab-associated ANCA glomerulonephritis: a case report and pathophysiology discussion. Case Rep Nephrol Dial 2021; 11: 376-383.
[45] Perazella MA and Sprangers B. AKI in patients receiving immune checkpoint inhibitors. Clin J Am Soc Nephrol 2019; 14: 1077-1079.
[46] Gupta S, Garcia-Carro C, Prosek JM, Glezerman I, Herrmann SM, Garcia P, Abudayyeh A, Lumlertgul N, Malik AB, Loew S, Beckerman P, Renaghan AD, Carlos CA, Rashidi A, Mithani Z, Deshpande P, Rangarajan S, Shah CV, Seigneux S, Campedel L, Kitchlu A, Shin DS, Coppock G, Ortiz-Melo DI, Sprangers B, Aggarwal V, Benesova K, Wanchoo R, Murakami N, Cortazar FB, Reynolds KL, Sise ME, Soler MJ and Leaf DE; ICPi-AKI Consortium Investigators. Shorter versus longer corticosteroid duration

and recurrent immune checkpoint inhibitor-associated AKI. J Immunother Cancer 2022; 10: e005646.
[47] Kalfeist L, Galland L, Ledys F, Ghiringhelli F, Limagne E and Ladoire S. Impact of glucocorticoid use in oncology in the immunotherapy era. Cells 2022; 11: 770.
[48] Manohar S, Ghamrawi R, Chengappa M, Goksu BNB, Kottschade L, Finnes H, Dronca R, Leventakos K, Herrmann J and Herrmann SM. Acute interstitial nephritis and checkpoint inhibitor therapy: single center experience of management and drug rechallenge. Kidney360 2020; 1: 16-24.
[49] Riveiro-Barciela M, Soler MJ, Barreira-Diaz A, Bermejo S, Bruera S and Suarez-Almazor ME. Expert clinical management of severe immune-related adverse events: results from a multicenter survey on hot topics for management. J Clin Med 2022; 11: 5977.
[50] Lee MD, Seethapathy H, Strohbehn IA, Zhao SH, Boland GM, Fadden R, Sullivan R, Reynolds KL and Sise ME. Rapid corticosteroid taper versus standard of care for immune checkpoint inhibitor induced nephritis: a single-center retrospective cohort study. J Immunother Cancer 2021; 9: e002292.
[51] Li J, Yu YF, Qi XW, Du Y and Li CQ. Immune-related ureteritis and cystitis induced by immune checkpoint inhibitors: case report and literature review. Front Immunol 2023; 13: 1051577.
[52] Jessel S, Austin M and Kluger HM. Mycophenolate as primary treatment for immune checkpoint inhibitor induced acute kidney injury in a patient with concurrent immunotherapy-associated diabetes: a case report. Clin Oncol Case Rep 2021; 4: 156.
[53] Qureshi S, Arani N, Parvathareddy V, Tchakarov A, Abdelrahim M, Suarez-Almazor M, Zhang J, Gibbons DL, Heymach J, Altan M and Abudayyeh A. Case report: immune checkpoint inhibitor-induced multiorgan vasculitis successfully treated with rituximab. Front Nephrol 2023; 3: 1168614.
[54] Ratanasrimetha P, Reddy VD, Kala J, Tchakarov A, Glass WF, Msaouel P and Lin JS. Case report: successful treatment of late-onset immune checkpoint inhibitor-associated membranous nephropathy in a patient with advanced renal cell carcinoma. Front Immunol 2022; 13: 898811.
[55] Parvathareddy V, Selamet U, Sen AA, Mamlouk O, Song J, Page VD, Abdelrahim M, Diab A, Abdel-Wahab N and Abudayyeh A. Infliximab for treatment of immune adverse events and its impact on tumor response. Cancers (Basel) 2023; 15: 5181.
[56] Abudayyeh A, Suo L, Lin H, Mamlouk O, Abdel-Wahab N and Tchakarov A. Pathologic predictors of response to treatment of immune checkpoint inhibitor-induced kidney injury. Cancers (Basel) 2022; 14: 5267.
[57] Tampe D, Baier E, Hakroush S and Tampe B. Serum sodium levels associate with recovery of kidney function in immune checkpoint inhibitor nephrotoxicity. Front Med (Lausanne) 2023; 10: 1020691.
[58] Peng L, Wang Y, Liu F, Qiu X, Zhang X, Fang C, Qian X and Li Y. Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors. Cancer Immunol Immunother 2020; 69: 1813-1822.
[59] Koda R, Watanabe H, Tsuchida M, Iino N, Suzuki K, Hasegawa G, Imai N and Narita I. Immune checkpoint inhibitor (nivolumab)-associated kidney injury and the importance of recognizing concomitant medications known to cause acute tubulointerstitial nephritis: a case report. BMC Nephrol 2018; 19: 48.
[60] Shirali AC. Is rechallenge appropriate in patients that develop immune checkpoint inhibitor-associated AKI?: COMMENTARY. Kidney360 2021; 3: 806-808.
[61] Rao Ullur A, Côté G, Pelletier K and Kitchlu A. Immunotherapy in oncology and the kidneys: a clinical review of the evaluation and management of kidney immune-related adverse events. Clin Kidney J 2023; 16: 939-951.
[62] Ai L, Gao J, Zhao S, Li Q, Cui YH, Liu Q, Wu D, Wang Y, Jin X, Ji Y, Li J, Yu Y and Liu T. Nivolumab-associated DRESS in a genetic susceptible individual. J Immunother Cancer 2021; 9: e002879.
[63] Sise ME, Seethapathy H and Reynolds KL. Diagnosis and management of immune checkpoint inhibitor-associated renal toxicity: illustrative case and review. Oncologist 2019; 24: 735-742.
[64] Pavan A, Calvetti L, Dal Maso A, Attili I, Del Bianco P, Pasello G, Guarneri V, Aprile G, Conte P and Bonanno L. Peripheral blood markers identify risk of immune-related toxicity in advanced non-small cell lung cancer treated with immune-checkpoint inhibitors. Oncologist 2019; 24: 1128-1136.
[65] Nagase K, Murai Y, Yokoyama-Kokuryo W, Nagasaka T, Sato Y, Watanabe T, Ito Y, Nagase F and Fujita Y. Renal immune-related adverse event of pembrolizumab masked by pemetrexed. Intern Med 2024; 63: 265-270.