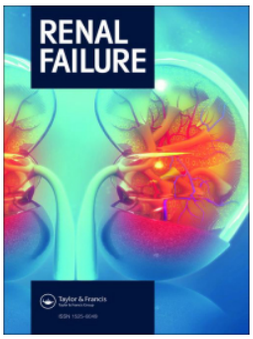

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CLINICAL STUDY

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Acute kidney injury in patients treated with immune checkpoint inhibitors: a single-center retrospective study

Ping Zhou[a*], Bing Liu[b*], Ning Shen[a], Xiaoting Fan[a], Shangwei Lu[b], Zhijuan Kong[b], Ying Gao[b], Zhimei Lv[a,b] and Rong Wang[a,b]

[a]Department of Nephrology, Shandong Provincial Hospital, Shandong University, Jinan, China; [b]Department of Nephrology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China

ABSTRACT

Background: Immune checkpoint inhibitor-associated acute kidney injury (ICI-AKI) is the most common renal complication and has attracted increasing amounts of attention. However, studies on this topic in Chinese cancer patients are very limited. Therefore, we conducted a retrospective study on the incidence, risk factors, clinical features and renal recovery of ICI-AKI in all patients with malignancies treated with ICIs in Shandong Provincial Hospital Affiliated to Shandong First Medical University.

Methods: In this single-center retrospective cohort study, the data of 904 patients who received immune checkpoint inhibitors (ICIs) treatment were retrospectively analyzed. Multivariable logistic regression was used to identify the predictors of ICI-AKI.

Results: A total of 46 of 904 patients receiving ICIs developed ICI-AKI, and the incidence of ICI-AKI was 5.1%. Patients developed ICI-AKI at a median of 9 weeks (IQR 3–23) after ICIs initiation. A lower baseline estimated glomerular filtration rate (eGFR) and use of antibiotics were associated with a higher risk of ICI-AKI. Renal recovery occurred in 17 patients (46%) at a median of 4 weeks (IQR 2–8) after ICI-AKI, including 16 (43%) with complete recovery and 1 (3%) with partial recovery. Of the 14 rechallenged patients, only one developed recurrent ICI-AKI.

Conclusions: Patients with ICI-AKI were more likely to have impaired renal function at baseline and after treatment with antibiotics. Approximately half of the patients achieved renal recovery.

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KEYWORDS
Acute kidney injury; immune checkpoint inhibitors; anti-PD-1 checkpoint inhibitors; immunotherapy; immune-related adverse events; malignancies

Background

As an antitumor therapy, immune checkpoint inhibitors (ICIs) have been widely used to treat advanced tumors, such as non-small cell lung cancer, renal cell carcinoma, and melanoma [1,2]. It promotes the activation of quiescent T cells (conventional T cells that are not activated) in lymph nodes (anti-CTLA4 checkpoint inhibitor) or impedes the failure of activated T cells by blocking the PD1 axis (anti-PD-1 checkpoint inhibitors) to enhance the antitumor response [2–5]. However, ICIs can improve the activity of the immune system and enhance the antitumor immune response but also lead to the loss of peripheral tolerance to autoantigens. That is, the normal tissues of other organs are also attacked by the immune system through autoimmune reactions known as immune-related adverse events (irAEs). Studies have shown that irAEs occur in multiple organs, including the skin, gastrointestinal tract, lung, endocrine system, musculoskeletal system, renal system, nervous system, hematologic system, and cardiovascular tract [6].

With the widespread use of ICIs, the effects of these agents on the kidney are of increasing concern. Acute kidney injury (AKI), known as immune checkpoint inhibitor-associated acute kidney injury (ICI-AKI), is the main adverse event in the kidney [7,8]. Previous studies have suggested that the development of ICI-AKI may be due to the binding of ICIs to checkpoint receptors expressed in the kidney to form haptens, called 'off-target effects' [9,10]. Previous studies have shown that the incidence of ICI-AKI ranges from 2.2% to 7.1% [9,11,12]. A lower baseline estimated glomerular filtration rate (eGFR), the use of proton pump inhibitors (PPIs) or antibiotics, combination ICIs therapy, and irAEs were associated with a higher risk of ICI-AKI [13–15]. In addition, previous studies have shown that early corticosteroid treatment is associated with a better prognosis [14,16,17] and more than half of patients with ICI-AKI achieve renal recovery, which may be due to the low stage of most ICI-AKI [14,18].

However, studies on ICI-AKI patients with malignancies treated with ICIs are rare in China. Based on the status quo,

CONTACT Zhimei Lv lvzhimei_sd@163.com; Rong Wang sd_wangrong@163.com Department of Nephrology, Shandong Provincial Hospital, Shandong University, Jinan, China; Department of Nephrology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China
*The authors have contributed equally.

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we conducted a study on the incidence, risk factors, clinical features, and renal recovery of ICI-AKI in all patients with malignancies treated with ICIs at Shandong Provincial Hospital affiliated with Shandong First Medical University. The objective of this study was to explore the incidence, risk factors and prognosis of ICI-AKI to provide a reference for the diagnosis and management of this disease and to improve the understanding of renal complications during antitumor therapy with ICIs.

Methods

Study design

In this single-center retrospective cohort study, we reviewed patients with malignant tumors who received ICIs treatment at Shandong Provincial Hospital Affiliated with Shandong First Medical University from December 2018 to October 2022 from the database established through the electronic medical records of the hospital. Patients were divided into ICI-AKI and non-AKI cohorts according to whether AKI occurred after ICI therapy and its etiology. The ICI-AKI follow-up time was defined as the period from ICIs initiation to ICI-AKI development and renal recovery within 90 days after ICI-AKI or the last follow-up. The median follow-up time was 20 (IQR, 8–30) weeks. Follow-up data were collected by reviewing the electronic medical records of the hospital. In our study, renal biopsy was not performed for any of the patients.

Data collection

Patients with malignant tumors were included if they met one of the following criteria: (1) were treated with ICIs alone without previous chemotherapy or (2) did not initiate ICIs treatment until more than 2 months after the end of chemotherapy. The major exclusion criteria included the following: (1) no serum creatinine (SCr) value before or after ICIs treatment; (2) dialysis at the time of ICIs initiation; and (3) a history of kidney transplant (Figure 1). Information on 904 patients was collected as follows: demographic information, including age, sex, comorbidities, history of nephrotoxic chemotherapy, and potentially nephrotoxic drugs; cancer type; ICIs type, including anti-PD-1 checkpoint inhibitors (camrelizumab, nivolumab, toripalimab, tislelizumab, pembrolizumab, and sintilimab) and anti-PD-L1 checkpoint inhibitors (atezolizumab), but not including anti-CTLA-4 checkpoint inhibitors; serum creatinine (SCr) (baseline, diagnosis, peak, ending) and other test results in different periods; treatment of ICI-AKI; and data on renal recovery and ICIs rechallenge.

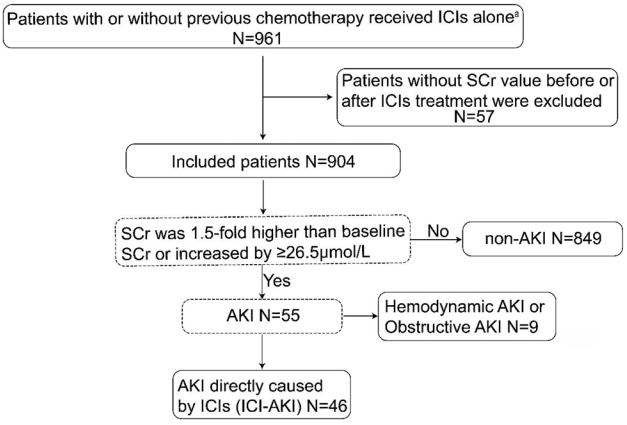

Figure 1. Flow chart of patient selection. [a] Patients with previous chemotherapy were defined as those with an interval of more than 2 months between subsequent ICIs, including cisplatin/carboplatin, oxaliplatin, gemcitabine, and tegafur. AKI: acute kidney injury; SCr: serum creatinine; ICIs: immune checkpoint inhibitors; ICI-AKI: immune checkpoint inhibitor-associated acute kidney injury.

Definition of ICI-AKI, renal recovery, and recurrent ICI-AKI

The criteria for ICI-AKI were as follows: (1) SCr was 1.5-fold higher than the baseline SCr or increased by ≥26.5 μmol/L; (2) after excluding hemodynamic AKI, including AKI that occurs in the context of dehydration, tumor lytic syndrome, sepsis, or ischemic acute tubular necrosis (ATN); and obstructive AKI, including all confirmed bilateral ureteral or urethral outlet obstruction; and (3) can be directly attributable to ICIs as assessed by at least two nephrologists (Figure 1). Referring to the Kidney Disease Improving Global Outcomes (KDIGO) [19,20], AKI was defined and staged for severity according to SCr changes. Specifically, AKI was defined as SCr was 1.5-fold higher than the baseline SCr or increased by ≥26.5 μmol/L. And the three stages s of AKI are as follows: stage 1: 1.5–1.9-fold increase in SCr from baseline or ≥26.5 μmol/L; stage 2: 2.0–2.9-fold increase in SCr from baseline; and stage 3: 3.0-fold increase in SCr from baseline or ≥353.6 μmol/L.

The baseline SCr level was defined as the value closest to but before ICIs initiation. Renal recovery was defined as SCr recovery to less than 1.5 times the baseline within 90 days after ICI-AKI [21], complete recovery was defined as SCr ≤26.5 μmol/L above baseline, and partial recovery was defined as SCr >26.5 μmol/L above baseline and <1.5 times baseline. Recurrent ICI-AKI after ICIs rechallenge was defined as a SCr level 1.5-fold higher than the new baseline SCr level (at the time of rechallenge) and was assessed by nephrologists to be attributable to ICIs.

Statistical analyses

All the statistical analyses were carried out using GraphPad Prism version 6.00 and IBM SPSS Statistics Version 26.0. Continuous data were compared using *t* tests or nonparametric tests, and categorical data were compared using nonparametric tests and the χ^2 test. Univariate analysis followed by multivariable logistic regression analysis using a stepwise variable selection procedure was used to determine the risk factors for ICI-AKI. In addition, we further analyzed the risk factors for ICI-AKI stratified by previous chemotherapy regimens using the same method. We reported odds ratios (OR) with 95% confidence intervals (CI) for the variables included in the univariate and multivariable models. $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Among the 904 patients with malignancies treated with ICIs, 684 patients (75.7%) were male, the median age of all 904 patients was 65 (IQR 58 to 69), and 884 patients (98%) received anti-PD-1 checkpoint inhibitors therapy. According to the diagnostic criteria, 46 patients (5.1%) were diagnosed with ICI-AKI, including 44 patients (5.0%) treated with anti-PD-1 checkpoint inhibitors and 2 patients (10.0%) treated with anti-PD-L1 checkpoint inhibitors.

Table 1 summarizes the baseline characteristics of these 46 patients and compares them with 849 patients without AKI. There was no significant difference in age or sex distribution between patients with ICI-AKI and those without AKI. Compared with patients without AKI, patients with ICI-AKI had a lower baseline eGFR and higher baseline SCr; were more likely to develop urogenital or gastrointestinal cancers; had comorbidities such as hypertension and chronic kidney disease (CKD); had greater exposure to antibiotics and diuretics. Notably, PPIs exposure was higher in both the ICI-AKI and the non-AKI cohorts (69.6% vs. 80.0%, respectively), but the difference was not significant ($p = 0.094$). In addition, no significant differences were found in age; sex; comorbidities such as diabetes, hepatitis/cirrhosis, CHF, CHD, cerebral hemorrhage/infarction, or gastrointestinal ulcer; ACEI/ARB and NSAIDs exposure; previous chemotherapy; or type of ICIs treatment.

Risk factors for ICI-AKI

According to the univariate logistic regression, ICI-AKI was associated with a lower baseline eGFR (OR 4.5; 95% CI 2.4 to 8.6; $p < 0.001$) and a history of hypertension (OR 1.9; 95% CI 1.0 to 3.4; $p = 0.042$). In addition, the use of antibiotics (OR 2.4; 95% CI 1.3 to 4.6; $p = 0.008$) and diuretics (OR 1.9; 95% CI 1.0 to 3.5; $p = 0.039$) was also associated with ICI-AKI. Furthermore, multivariable logistic regression of the above factors was carried out by using the forward conditional method, and it was concluded that ICI-AKI was still associated with lower baseline eGFR (OR 4.7; 95% CI 2.4 to 8.9; $p < 0.001$) and the use of antibiotics (OR 2.7; 95% CI 1.4 to 5.3; $p = 0.003$) (Figure 2). However, more than half of the patients in our study had previously received chemotherapy. Therefore, to minimize bias, we performed analyses stratified according to previous chemotherapy regimens, and the results showed that ICI-AKI was still associated with lower baseline eGFR (OR 4.8, 3.7; 95% CI 2.1 to 10.6, 1.2 to 12.0; $p < 0.001$, $p = 0.028$) (Figure S1).

Table 1. Characteristics of the population at baseline. All the data are complete.

Variable	All	ICI-AKI	non-AKI	*p*
No. of patients	904	46	849	
Age, median (IQR) (years)	65 (58–69)	62 (53–72)	65 (58–69)	0.463
Female, n (%)	220 (24.3)	8 (17.4)	208 (24.5)	0.376
Comorbidities, n (%)				
Hypertension	289 (32.0)	21 (45.7)	264 (31.1)	0.050
Diabetes	154 (17.0)	9 (19.6)	142 (16.7)	0.551
CKD	10 (1.1)	2 (4.3)	8 (0.9)	0.089
Cirrhosis/Hepatitis	101 (11.2)	8 (17.4)	92 (10.8)	0.224
CHF	7 (0.8)	0 (0)	7 (0.8)	1.000
CHD	112 (12.4)	5 (10.9)	103 (12.1)	0.981
Cerebral hemorrhage/cerebral infarction	75 (8.3)	1 (2.2)	73 (8.6)	0.168
gastrointestinal ulcer	41 (4.5)	3 (6.5)	38 (4.5)	0.463
Baseline SCr, μmol/L	61.5 (53.0–70.1)	70.5 (61.9–85.7)	60.9 (52.7–69.6)	**<0.001**
Baseline eGFR, mL/min	104 (96.0–112.0)	98 (83.8–105.8)	104 (96.0–113.0)	**<0.001**
Baseline eGFR categories, n (%)				**<0.001**
<90 mL/min	115 (12.7)	17 (37.0)	97 (11.4)	
≥90mL/min	789 (87.3)	29 (63.0)	752 (88.6)	
Drugs, n (%)				
PPIs	715 (79.1)	32 (69.6)	679 (80.0)	0.094
ACEI/ARB	111 (12.3)	9 (19.6)	101 (11.9)	0.161
Antibiotics	450 (49.8)	32 (69.6)	414 (48.8)	**0.006**
Diuretics	434 (48.0)	29 (63.0)	401 (47.2)	**0.048**
NSAIDs	458 (50.7)	27 (58.7)	426 (50.2)	0.291
Previous chemotherapy[a], n (%)	564 (62.4)	31 (67.4)	529 (62.3)	0.535
Malignancy, n (%)				**<0.001**
Lung	376 (41.6)	13 (28.3)	363 (42.8)	
Gastrointestinal	495 (54.8)	27 (58.7)	466 (54.9)	
Urogenital	18 (2.0)	3 (6.5)	9 (1.1)	
Other	15 (1.7)	3 (6.5)	11 (1.3)	
ICIs, n (%)				0.275
Anti-PD-1	884 (97.8)	44 (95.7)	831 (97.9)	
Anti-PD-L1	20 (2.2)	2 (4.3)	18 (2.1)	

The data are shown as the median (IQR) and n (%). Bold values are statistically significant.[a]Prior chemotherapy was defined as an interval of more than 2 months between subsequent ICIs, including cisplatin/carboplatin, oxaliplatin, gemcitabine, and tegafur. ICI-AKI: immune checkpoint inhibitor-associated acute kidney injury; CKD: chronic kidney disease; CHF: congestive heart failure; CHD: coronary atherosclerotic heart disease; SCr: serum creatinine; eGFR: estimated glomerular filtration rate; PPIs proton pump inhibitors; ACEI, :antensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers; NSAIDs: nonsteroidal anti-inflammatory drugs; ICIs: immune checkpoint inhibitors; PD-1: programmed cell death 1; PD-L1: programmed death-ligand 1.

Variables	Univariate analysis p Value[a]	Univariate analysis OR (95%CI)	Multivariable analysis p Value	Multivariable analysis OR (95%CI)
Age	0.380	0.986 (0.954-1.018)		
Female	0.276	0.649 (0.298-1.413)		
eGFR categories				
⩾90 (REF)		1		1
<90	**<0.001**	**4.545 (2.409-8.575)**	**<0.001**	**4.655 (2.434-8.903)**
CKD	0.052	4.778 (0.985-23.172)		
Cirrhosis/Hepatitis	0.174	1.732 (0.784-3.827)		
Hypertension	**0.042**	**1.861 (1.023-3.385)**		
Diabetes	0.617	1.211 (0.572-2.565)		
CHD	0.798	0.883 (0.341-2.286)		
cerebral hemorrhage/cerebral infarction	0.157	0.236 (0.032-1.739)		
gastrointestinal ulcer	0.521	1.489 (0.442-5.017)		
PPIs	0.092	0.572 (0.299-1.096)		
ACEI/ARB	0.128	1.801 (0.845-3.842)		
Antibiotics	**0.008**	**2.402 (1.263-4.565)**	**0.003**	**2.706 (1.394-5.254)**
Diuretics	**0.039**	**1.906 (1.032-3.520)**		
NSAIDs	0.262	1.411 (0.773-2.577)		
Previous chemotherapy[b]	0.489	1.250 (0.665-2.352)		
ICIs				
PD-1 (REF)		1		
PD-L1	0.330	2.098 (0.472-9.330)		

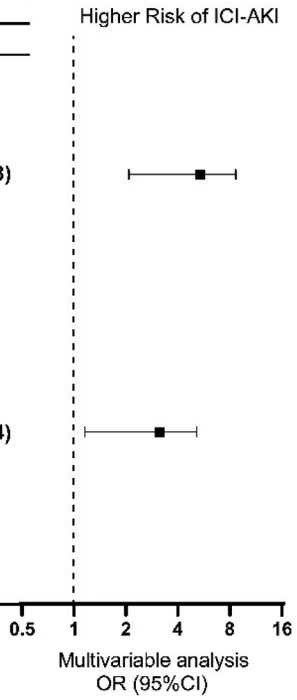

Figure 2. Risk factors for ICI-AKI. A total of 895 patients were included; 46 had ICI-AKI and 849 had non-AKI. [a] Only variables with $p < 0.05$ according to univariate logistic regression analysis were analyzed *via* multivariable logistic regression. [b] Prior chemotherapy was defined as an interval of more than 2 months between subsequent ICIs, including cisplatin/carboplatin, oxaliplatin, gemcitabine, and tegafur. Bold values are statistically significant. ICI-AKI, immune checkpoint inhibitor-associated acute kidney injury; eGFR: estimated glomerular filtration rate; REF: reference; CHD: coronary atherosclerotic heart disease; PPIs: proton pump inhibitors; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin-receptor blockers; NSAIDs: nonsteroidal anti-inflammatory drugs; ICIs: immune checkpoint inhibitors; PD-1: programmed cell death 1; PD-L1: programmed death-ligand 1, OR: odds ratio; CI: confidence interval.

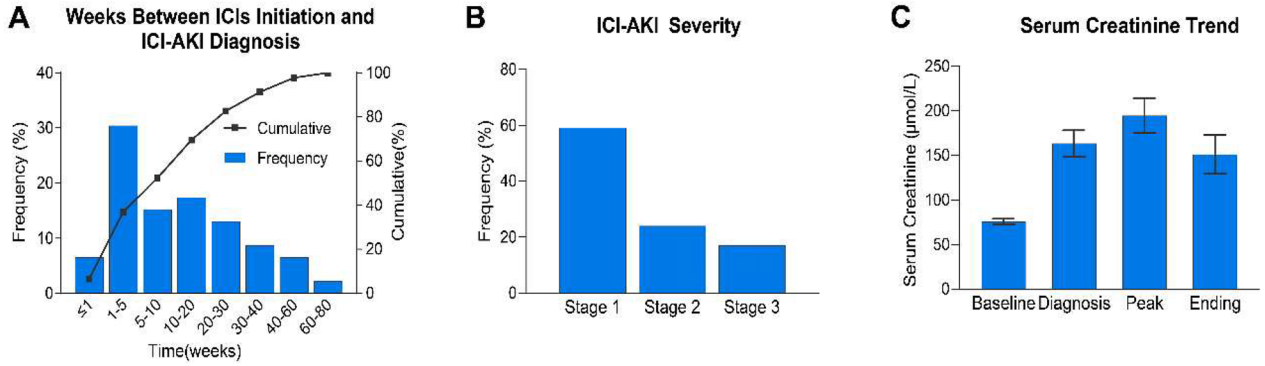

Figure 3. Clinical features of ICI-AKI. (A) The number of weeks between ICIs initiation and ICI-AKI diagnosis. (B) The distribution of ICI-AKI severity according to the Kidney Disease Improving Global Outcomes criteria. (C) The trend in SCr levels (mean ± SEM). The baseline SCr level was defined as the value closest to but before ICIs initiation; the diagnosis SCr refers to the value at which the patient first fulfilled the criteria for ICI-AKI; the peak SCr refers to the highest value during the AKI episode; and ending SCr is the value at the time of renal recovery (for patients with renal recovery) or the most recent value available after AKI diagnosis (for patients without renal recovery). ICIs, immune checkpoint inhibitors; ICI-AKI, immune checkpoint inhibitor-associated acute kidney injury; SCr, serum creatinine.

Clinical features of ICI-AKI

Patients developed ICI-AKI at a median of 9 weeks (IQR 3–23) after ICIs initiation (Figure 3A). According to KDIGO's definition and grading criteria for AKI, of the 46 patients diagnosed with ICI-AKI, 27 (59%) had stage 1 AKI, 11 (24%) had stage 2 AKI, and 8 (17%) had stage 3 AKI (Figure 3B). Among patients with severe ICI-AKI, no patient required renal replacement therapy. The SCr value for each period, including baseline, AKI diagnosis, peak, and ending results, is recorded in Figure 3C.

The concomitant medication regimens and clinical test results (after ICIs treatment) of the ICI-AKI patients are shown in Figure 4 and were stratified according to the severity of AKI. During the course of ICI treatment, the vast majority of

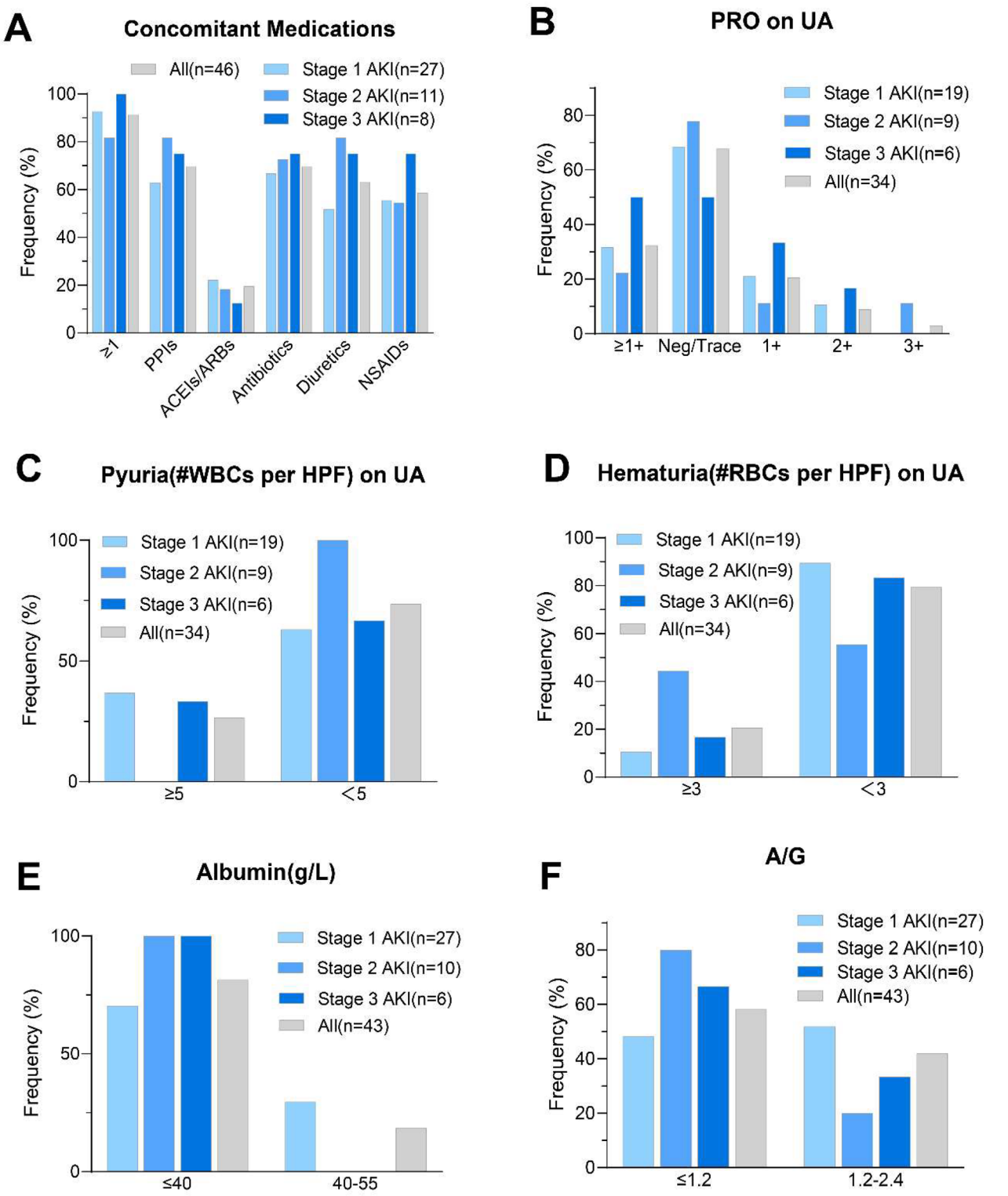

Figure 4. Clinical features of ICI-AKI patients stratified by severity. (A) The frequency of combination therapy with other medications during ICIs treatment. (B-K) The distributions of urine protein levels, pyuria, hematuria, blood albumin levels, the albumin-to-globulin ratio (A/G), URIC, eosinophilia, the urea nitrogen-to-creatinine ratio (BUN/CREA) and urine glucose in patients with ICI-AKI. AKI: acute kidney injury; ICI-AKI immune checkpoint inhibitor-associated acute kidney injury; PPIs: proton pump inhibitors; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin-receptor blockers; NSAIDs: nonsteroidal anti-inflammatory drugs; PRO: protein; UA: urinalysis; Neg: negative; WBCs: white blood cells; HPF: high-power field; RBCs: red blood cells; A/G: albumin-to-globulin ratio; URIC: uric acid; BUN/CREA: urea nitrogen-to-creatinine ratio; GLU: urine glucose.

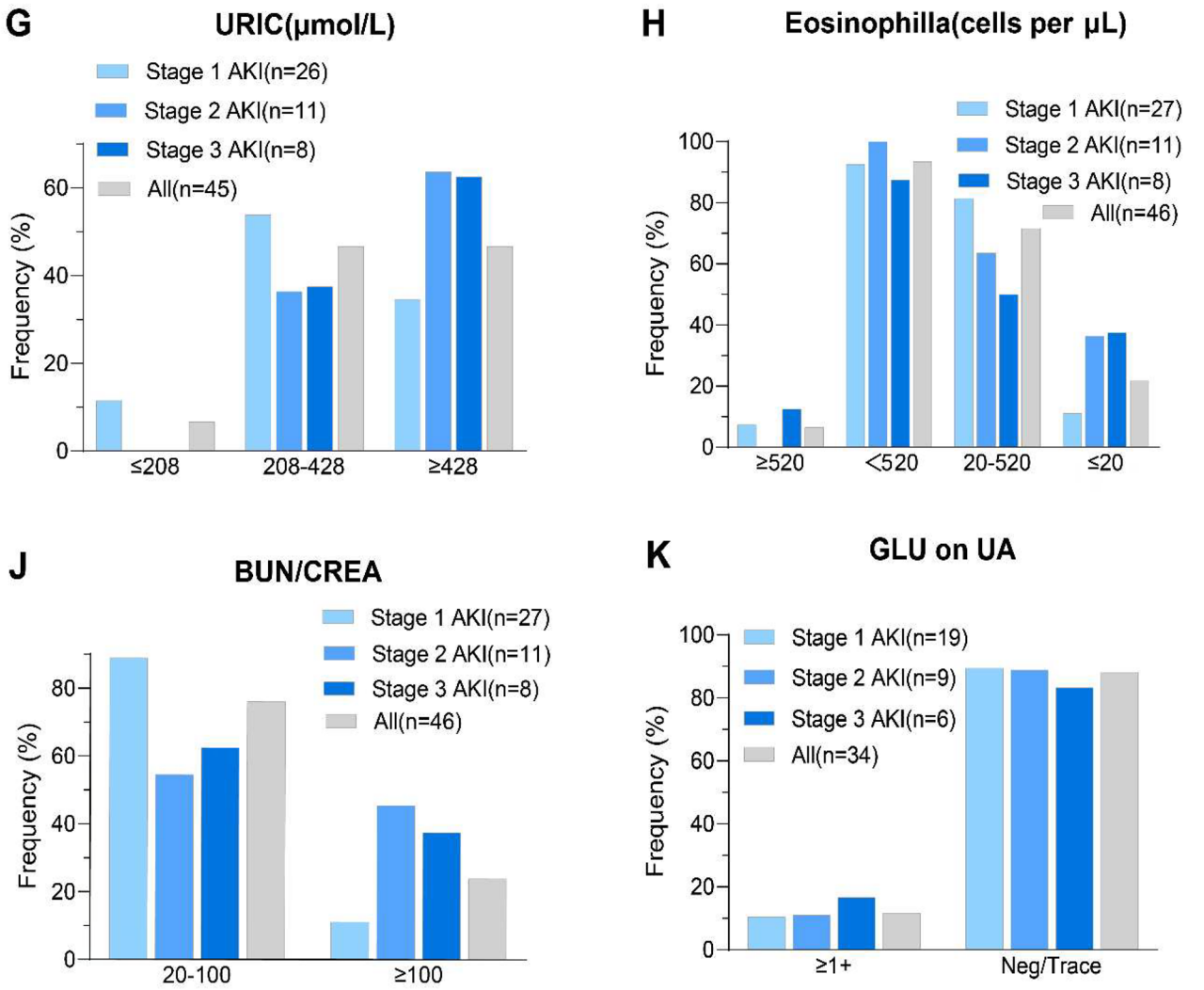

Figure 4. Continued.

patients (91%) were taking combination medications known to cause acute interstitial nephritis (AIN) or alter renal hemodynamics; these included antibiotics, NSAIDs, PPIs, diuretics, and ACEIs/ARBs, with PPIs and antibiotics accounting for the highest proportion (69.6%) of patients (Figure 4A). Nearly one-third of patients (32%) had positive urine protein levels, most of which were 1+ (Figure 4B); routine urine test results revealed pyuria in 26% of patients (Figure 4C) and hematuria in 21% of patients (Figure 4D); approximately 81% of patients (Figure 4E) had lower-than-normal blood albumin levels; the albumin-to-globulin ratio (A/G) was below the lower limit of normal in approximately half of the patients (58%) (Figure 4F); and uric acid (URIC) was higher than normal in 47% of all patients and was even higher in stage 2 or 3 patients (63%) (Figure 4G). Most patients did not have eosinophilia (93%) (Figure 4H). Similarly, the urea nitrogen-to-creatinine ratio (BUN/CREA) (76%) (Figure 4J) was within the normal range and urine glucose (88%) (Figure 4K) was negative in the majority of patients. In contrast, patients with higher AKI stages were more likely to have abnormal urine glucose and urine protein levels and increased eosinophilia according to blood analysis.

Treatment of ICI-AKI and renal recovery after ICI-AKI

In our study, corticosteroid treatment for ICI-AKI was individualized and empirical. Among the 46 patients with ICI-AKI, 15 patients received corticosteroids for ICI-AKI, including 7 patients (47%) with stage 1 AKI, 4 patients (26.5%) with stage 2 AKI, and 4 patients (26.5%) with stage 3 AKI. In addition, 12 patients were treated with ICIs in combination with corticosteroids (Table S1). The median renal recovery time after ICI-AKI diagnosis was 4 weeks (IQR 2–8) (Figure 5A). Overall, of the 37 ICI-AKI patients with documented ending SCr levels, 20 patients (54%) experienced no renal recovery, and 17 patients (46%) experienced renal recovery—16 patients (43%) with complete recovery and 1 patient (3%) with partial recovery. After the development of ICI-AKI, patients who received corticosteroids had a greater rate of renal recovery than did those who did not (62% vs. 38%). Of the 17 patients who achieved renal recovery, 71% were initially in AKI stage 1, 12% were in AKI stage 2, and 17% were in AKI stage 3 (Figure 5B). The characteristics of renal recovery patients and patients without renal recovery are described in Supplemental Table S2. There were significant differences in coexisting hypertension

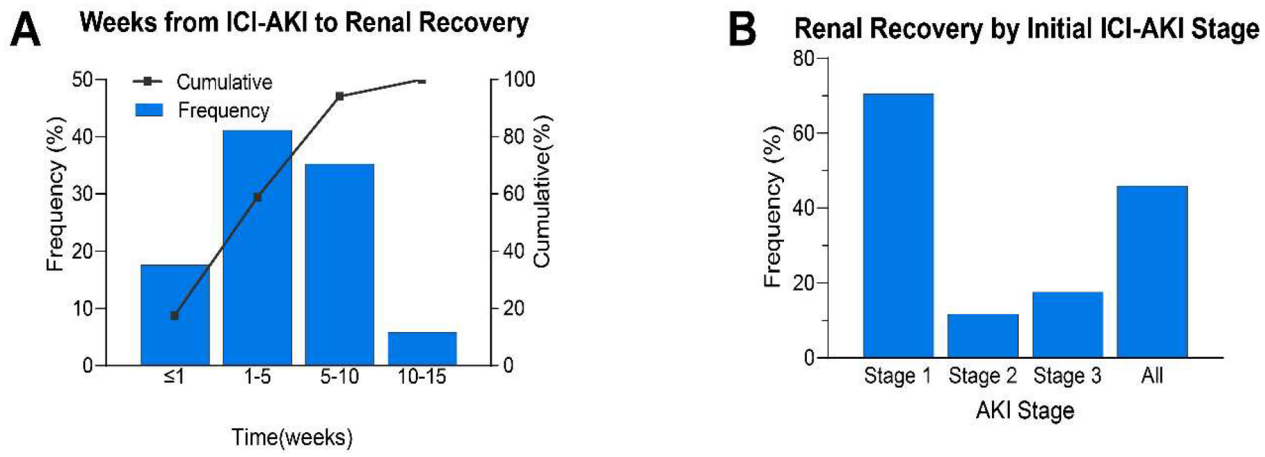

Figure 5. Characteristics of renal recovery in patients with ICI-AKI. (A) Time (in weeks) from ICI-AKI diagnosis to renal recovery. (B) Renal recovery overall and according to initial ICI-AKI stage. Patients without an ending scan of SCr ($n = 9$) were excluded. ICI-AKI, immune checkpoint inhibitor-associated acute kidney injury; AKI, acute kidney injury.

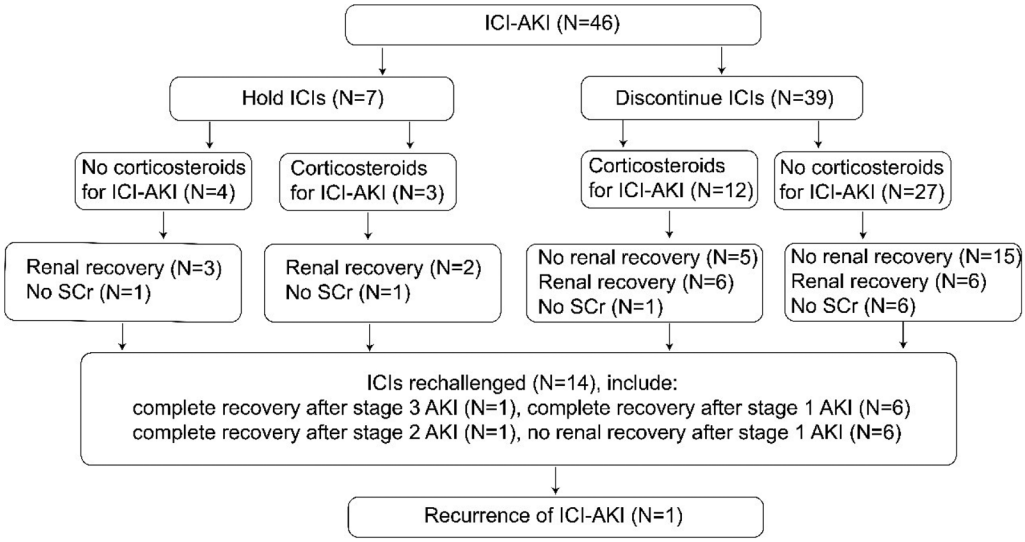

Figure 6. Flow chart of the rates of treatment with corticosteroids, renal recovery, rechallenge, and AKI recurrence. ICI-AKI: immune checkpoint inhibitor-associated acute kidney injury; AKI: acute kidney injury; SCr: serum creatinine; ICIs: immune checkpoint inhibitors.

($p = 0.049$), exposure to PPIs ($p = 0.036$) and ending SCr ($p < 0.001$).

Rechallenge of patients with ICI-AKI

Of 37 patients with ICI-AKI with available SCr, 14 (38%) patients were rechallenged with ICIs, and the median rechallenge time after ICI-AKI diagnosis was 11 weeks (IQR 8–22). Among these patients, only 1 patient (complete recovery after initial stage 3 AKI) developed recurrent ICI-AKI (Figure 6). This patient developed recurrent stage 1 AKI, and the recurrence time was 81 days, which was shorter than the first AKI occurrence time (132 days). In addition, there were 5 patients with varying degrees of SCr elevation (lower than the diagnostic criterion for AKI recurrence). Among them, 1 patient completely recovered after the initial stage 3 AKI, 1 patient completely recovered after the initial stage 1 AKI, and 3 patients did not recover after the initial stage 1 AKI.

Discussion

In this single-center retrospective study, we evaluated the incidence, risk factors, clinical features, and renal recovery outcomes of ICI-AKI. First, for the context of our study institution, we concluded that the incidence of ICI-AKI was 5.1%. The incidence of ICI-AKI varied among studies [11,14,22–24], possibly because ICI-AKI was defined differently in different studies or because hemodynamic AKI or obstructive AKI was included due to a lack of exclusion [22]. The high proportion

of patients (62%) who had previously received chemotherapy in our study may also have contributed to the greater incidence of ICI-AKI in our study than in other studies. Second, we found that lower baseline eGFR and the use of antibiotics were associated with a higher risk of ICI-AKI. Third, for patients with ICI-AKI, more than half of the patients had stage 1 AKI. Moreover, pyuria, hematuria and urine protein were present in less than one-third of the patients. Notably, the serum albumin concentration was less than normal in most patients. Fourth, we found renal recovery in approximately half of the patients, with complete recovery in the vast majority of patients. Of the 14 patients rechallenged with ICIs, only one developed recurrent AKI (stage 1 AKI).

Consistent with the findings of previous studies, we found that a lower baseline eGFR was associated with the development of ICI-AKI [13,14,25,26]. However, some studies have shown that baseline eGFR is not associated with the development of ICI-AKI [12,23,27,28]. One explanation is that the former may have been influenced by other confounding factors, such as age and cardiovascular disease [29], which were also difficult to rule out in our study. An alternative explanation is that patients with lower baseline eGFRs have poorer renal reserves, which raises the threshold of SCr rather than increases the risk of immune damage from ICIs [13,26]. In addition, we found that the use of antibiotics was also a risk factor for ICI-AKI. Previous studies have shown that retreatment with ICIs after exposure to drugs known to cause AIN (PPIs, NSAIDs, and antibiotics) activates drug-specific T cells, leading to loss of tolerance[14,30].

As in previous studies [24,31–33], we found a lower percentage of patients with pyuria, hematuria, proteinuria, and eosinophilia. These noninvasive markers revealed renal involvement [34]. However, these criteria are not specific to kidney disease and therefore cannot be used alone as a basis for a definitive diagnosis of ICI-AKI. Similarly, although we found hypoproteinaemia in the majority of patients, we could not distinguish whether this was related to cancer cachexia syndrome [35] or AKI [36]. We found that ICI-AKI occurred at a median time of 9 weeks, which is different from the findings of other studies, indicating that the latency between ICIs initiation and ICI-AKI is highly variable [13,14,24,34]. Compared with the onset time of extrarenal irAEs, the latency of ICI-AKI was longer [25,37,38], which may be related to the delay in clinical recognition due to the insensitivity of SCr to kidney injury [38].

In our study, ICI-AKI recurred in only 1 of 14 patients who underwent rechallenge. Although the data are limited, together with the findings of other studies, we found a low recurrence rate of ICI-AKI [12,13,39]. Therefore, we believe that rechallenge with ICIs can be considered after detailed evaluation in patients for whom ICIs are the best antitumor treatment.

This study evaluated ICI-AKI in a larger cohort of Chinese patients treated with ICIs (primarily anti-PD-1 checkpoint inhibitors). However, in China, more attention has been given to the antitumor treatment plan and efficacy for patients who choose ICI therapy, and renal biopsy, an invasive diagnostic method, cannot be widely accepted. Therefore, renal biopsy data were lacking in our cohort, which limited the understanding of the underlying pathophysiological mechanisms of ICI-AKI. However, previous reports have shown that the major histopathological type of renal biopsy sample is acute tubulointerstitial nephritis (ATIN) [13,26,31,40]. Many studies have identified biomarkers of ICI-AKI, including serum C-reactive protein (CRP), IL-17, tumor necrosis factor-α, the urine retinol binding protein-to-creatinine ratio, and urine sCD163 [7,26,38,39]. However, their use in the diagnosis of ICI-AKI needs to be further confirmed by additional studies. In our study, further classification was not possible due to the lack of data on renal biopsy and clinical characteristics. Similarly, in the study of risk factors for ICI-AKI, we had no conclusions regarding PPIs or extrarenal irAEs because our cohort had a high proportion of patients receiving PPIs and a relatively small sample size; moreover, hospital electronic medical records lacked documentation of extrarenal irAEs, which is also a limitation of our study. In addition, another limitation is the use of a single SCr value to calculate baseline kidney function in our study, which can lead to misclassification by including missed cases of community-acquired AKI. A better definition would be the mean of all SCr levels in the 6 months prior to ICIs initiation, but in our study, these data were not available in the electronic medical records of the hospitals. We must acknowledge that we did not establish a control cohort in which patients did not receive ICIs, which limits the ability to ascertain the direct effect of ICIs on renal injury; this is also a limitation of our study. Finally, we will continue the study on mortality in the next step.

This study explored the incidence, clinical characteristics, risk factors, and overall outcome of ICI-AKI in a large cohort of Chinese patients, which may inform the use of anti-PD-1 checkpoint inhibitors in the real world. In the future, randomized controlled trials with larger samples are needed to further confirm and study the mechanism of ICI-AKI to help clinicians diagnose ICI-AKI more clearly.

Conclusions

In summary, the incidence of ICI-AKI in this real-world cohort study was 5.1%. Patients with ICI-AKI were more likely to have impaired renal function at baseline and to use antibiotics. Approximately half of the patients achieved renal recovery after ICI-AKI. This was a single-center retrospective study in which patients were treated with anti-PD-1 checkpoint inhibitors in the real world. However, further multicenter collaborative studies are needed to provide additional evidence for the management of ICI-AKI patients.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Shandong Provincial Hospital affiliated to Shandong First Medical University (approval number: SWYX:NO.2023-438). Informed consent was waived with the approval of the ethics committee.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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