CKJ REVIEW

The association between acute kidney injury and outcomes in cancer patients receiving immune checkpoint inhibitor therapy: a systematic review and meta-analysis

Mehmet Kanbay [1], Sidar Copur[2], Dimitrie Siriopol[3], Abdullah Burak Yildiz [2], Metehan Berkkan[2], Raluca Popa[3], Nuri Baris Hasbal [1], Alberto Ortiz [4] and Mark A. Perazella[5]

[1]Department of Medicine, Section of Nephrology, Koc University School of Medicine, Istanbul, Turkey, [2]Department of Medicine, Koc University School of Medicine, Istanbul, Turkey, [3]Department of Nephrology, "Saint John the New" County Hospital, Suceava, Romania, [4]Department of Medicine, Universidad Autonoma de Madrid and IIS-Fundacion Jimenez Diaz, Madrid, Spain and [5]Department of Internal Medicine Section of Nephrology, Yale University School of Medicine, CT, USA

Correspondence to: Mehmet Kanbay; E-mail: drkanbay@yahoo.com, mkanbay@ku.edu.tr

ABSTRACT

Background. Immune checkpoint inhibitors (ICPIs) are a novel therapeutic approach to cancer treatment that have changed the landscape of cancer therapy but also have some considerable drawbacks. Acute kidney injury (AKI) is one of these potential complications that may have effects on patient outcomes. In this review, we assessed the effect of AKI on mortality outcomes in cancer patients receiving this immunotherapy.

Methods. We performed a systematic review and meta-analysis of prospective, retrospective, randomized and non-randomized studies, which examined the effects of AKI in cancer patients receiving immune checkpoint inhibitors. We searched through PubMed, Medline, Web of Science, Scopus and Cochrane Library databases.

Results. Seven studies were included in the final analysis, with a total number of patients of 761. Overall, the risk of death was higher in patients that developed AKI during ICPI treatment [hazard ratio (HR) 1.42, 95% confidence interval (CI) 1.05–1.92, $P = 0.02$; heterogeneity $\chi^2 = 11.68$, $I^2 = 66\%$, $P = 0.02$] compared with patients that did not develop AKI. In addition, there was a trend to a better survival in those with less severe AKI patients compared with those with more severe AKI (HR 1.35, 95% CI 0.99–1.83, $P = 0.05$). Lastly, it was seen that patients with persistent kidney dysfunction (non-recovery) had an increased risk for all-cause mortality (HR 2.93, 95% CI 1.41–6.08, $P = 0.004$; heterogeneity $\chi^2 = 0.53$, $I^2 = 0\%$, $P = 0.47$).

Conclusions. Development of AKI in patients with cancer receiving immune checkpoint inhibitors is associated with increased risk of mortality.

LAY SUMMARY

Immune checkpoint inhibitors are a novel therapeutic approach to cancer treatment that have changed the landscape of cancer therapy but also have some considerable drawbacks. Acute kidney injury (AKI) is one of these potential complications that may have effects on patient outcomes. In this review, development of AKI in patients with cancer receiving immune checkpoint inhibitors is associated with increased risk of mortality.

INTRODUCTION

Immune checkpoint inhibitors (ICPIs) act primarily to inhibit the down-regulatory immune system pathways that suppress the host's immune response. The immune checkpoints involved in this balance of stimulatory and inhibitory pathways include the programmed cell death 1 (PD-1) receptors or its ligand (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) receptors [1, 2]. The implementation of ICPIs has been subsequently shown to improve cancer therapy in terms of the treatment outcomes including progression-free survival and overall survival [3, 4]. Despite being primarily a supportive approach to mainstay treatments (chemotherapy, targeted therapies and radiotherapy), immunotherapy is a beacon of hope for many patients and ICPIs have already become one of the main pillars in cancer treatment [5–7].

The use of ICPIs in the treatment of certain malignancies contributes greatly to improved patient prognosis; however, activation of the immune system has potential drawbacks which are referred as immune-related adverse events (IRAEs) [8]. This concept is similar to autoimmune diseases, which are the direct result of the overactivation of immune system by ICPIs [3, 8, 9]. Skin, gastrointestinal tract and liver are the sites most commonly affected by IRAEs; nevertheless, nearly all tissues and organs including the lungs, nervous system, endocrine organs, joints, heart, pancreas and the kidneys may be involved at any time point during or after immunotherapy [8, 9]. Although most IRAEs are mild and reversible with the discontinuation of the responsible agent, life-threatening IRAEs have also been reported [8, 9]

Acute kidney injury (AKI) that develops in cancer patients in the setting of ICPI has been investigated, though most of the published data are limited to case reports, case series and a small number of cohort studies. Biopsy-proven acute interstitial nephritis, which is the most commonly observed lesion along with acute tubular injury/necrosis, and a variety of glomerular diseases have been reported in a small number of studies. The prognostic importance of AKI in the treatment of many medical conditions has been well established in large-scale studies [10–12], whereas the true incidence of AKI and its effect on mortality in patients receiving immunotherapy is unclear due to lack of comprehensive studies and meta-analysis. With this background, this systematic review and meta-analysis aims to assess the impact of AKI in patients with cancer receiving ICPIs on long-term prognosis focusing on mortality.

MATERIALS AND METHODS

In this systematic analysis and meta-analysis, guidelines of the Cochrane Collaboration and Meta-Analysis of Observational Studies in Epidemiology (MOOSE), Quality of Reporting of Meta-Analyses (QUOROM) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed [13–15].

Data source and strategy

The literature search has been performed through five databases including PubMed, Medline, Web of Science, Scopus and Cochrane Library databases by utilizing the listed terms or their combinations: 'acute kidney injury', 'acute kidney failure', 'acute renal failure', 'nephrotoxicity', 'immune checkpoint', 'immune checkpoint inhibitors', 'immunotherapy', 'atezolizumab', 'nivolumab', 'pembrolizumab', 'iplimumab', 'avelumab', 'durvalumab', 'cemiplimab', 'PD-1 inhibitor', 'PD-L1 inhibitor' and 'CTLA-4 inhibitor' (Supplementary data, Table S1). Three investigators (A.B.Y., M.B., S.C.) screened abstracts and titles of the studies that were reached through the search platforms mentioned above. Bibliographies of the reviews and studies were additionally screened for relevant publications. The selected studies were further investigated by three investigators (A.B.Y., M.B., S.C.) in full text, for relevance of the specified criteria. Furthermore, references listed on selected studies and reviews were assessed manually for additional relevant studies. After the preliminary selection, full texts of the selected studies were independently evaluated by the authors. Details of study selection procedures are depicted in Supplementary data, Table S1. Data extraction was performed by three authors (A.B.Y., M.B., S.C.), with the extracted properties being study characteristics (year, author, study design), inclusion/exclusion criteria, population characteristics (age, sex, ICPi distribution), ICPI therapy length, follow-up length, AKI incidence, outcomes of AKI and non-AKI patients and severity of AKI. Relevant information extracted according to these properties is demonstrated in Tables 1 and 2. The study selection and assessment process has been evaluated in detail through PRISMA flowchart on Fig. 1.

Most studies included in this meta-analysis study utilized the Kidney Disease: Improving Global Outcomes (KDIGO) criteria and staging for AKI, whereas differences in terms of such definitions exist across individual studies such as inclusion of biopsy as a diagnostic criteria or clinical diagnosis of AKI etiology.

Inclusion and exclusion criteria

All cohort studies conducted on patients with cancer receiving ICPIs and reported the outcomes of patients both developing or not developing AKI are included in this meta-analysis regardless of their randomization process or being prospective or retrospective. Outcomes are considered as death rate, overall recovery rate and also severity according to the AKI stage.

Duplicates of the studies, repetitive results, reviews, case studies and meta-analyses were excluded. Studies with patient

Table 1: General characteristics of the included studies.

Study name [ref], year, continental area	Study type	(i) Inclusion criteria; (ii) exclusion criteria	Total cohort (N)	Male [n (%)]	Age (years)	Follow-up length (weeks)	ICPi distribution [n (%)]
Cortazar et al. [20] 2020, North America	Retrospective cohort	(i) Patients with ICPi-AKI if the AKI was attributed directly to the ICPi and patients had at least a doubling of serum creatinine or the requirement for RRT; (ii) NA	414	254 (61)	66 (mean)	29 (median)	Anti-CTLA-4, n = 92 (22.2%); anti-PD-1, 377 (91%); anti-PD-L1, 23 (5.5%); combination, 74 (17.8%)
García-Carro et al. [24] 2022, Europe	Retrospective cohort	(i) All patients >18 years of age; (ii) end-stage kidney disease and with previous kidney transplant	759	449 (59)	64 (mean)	25 (median)	Anti-CTLA-4. 9 (1.2%); anti-PD-1. 422 (55.6%); anti-PD-L1. 207 (27.3%); combination. 8 (1%); others.33 (4.3%)
Gupta et al. [19] 2021, North America/Europe/Asia	Retrospective cohort	(i) Patients with ICPi-AKI if the AKI was attributed directly to the ICPi and patients had at least a doubling of serum creatinine or the requirement for RRT; (ii) end-stage kidney disease and with previous kidney transplant	858	517 (60.2)	ICPi-AKI = 68 (median); n on-ICPi-AKI = 65 (median)	30 (median)	Anti-CTLA-4, 198 (23%); anti-PD-1, 702 (81.8%); anti-PD-L1, 72 (8.4%); combination, 174 (20%)
Koks et al. [23] 2021, Europe	Retrospective cohort	(i) >18 years of age and taken nivolumab, ipilimumab, pembrolizumab, atezolizumab, durvalumab, or tremelimumab; (ii) patients on renal replacement therapy, without serum creatinine measurement in the 12 months prior to first ICPi administration, or without any serum creatinine measurement after first ICPi administration	676	420 (62)	64 (median)	36 (median)	Nivolumab, 202 (29.9%); ipilimumab, 45 (6.7%); pembrolizumab, 236 (34.9%); Nivo + Ipi, 132 (19.5%); others, 61 (9%)

Table 1: Continued.

Study name [ref], year, continental area	Study type	(i) Inclusion criteria; (ii) exclusion criteria	Total cohort (N)	Male [n (%)]	Age (years)	Follow-up length (weeks)	ICPi distribution [n (%)]
Meraz-Muñoz et al. [21] 2020, North America	Retrospective cohort	(i) >18 years of age received at least one dose of ipilimumab, nivolumab or pembrolizumab; (ii) end-stage kidney disease on dialysis or with previous kidney transplant	309	186 (60)	61 (median)	37 (median)	Ipilimumab, 219 (70.9%); nivolumab, 54 (17.5%); pembrolizumab, 36 (11.7%); Nivo + Ipi, 23 (7.4%)
Seethapathy et al. [22] 2020, North America	Retrospective cohort	(i) Patients received PD-L1 inhibitors; (ii) patients do not have a baseline or a follow-up creatinine within 12-month follow-up and on hemodialysis	599	298 (50)	65 (mean)	NA	Atezolizumab, 347 (58%); durvalumab, 153 (26%); avelumab, 99 (16%)
Shimamura et al. [18] 2021, Asia	Retrospective cohort	(i) Patients who initiated ICPi for malignancies; (ii) patients with contrast-induced nephropathy	152	114 (75)	67 (mean)	NA	Nivolumab, 79 (52%); pembrolizumab, 55 (35%); atezolizumab, 10 (7%); durvalumab, 8 (5%); ipilimumab, 2 (1%); Nivo + Ipi: 2 (1%)

NA, not applicable; ICPi-AKI, immune checkpoint inhibitor–induced acute kidney injury; Nivo + Ipi, nivolumab + ipilimumab.

Table 2: Outcomes of the included studies.

Study name [ref] year, continental area	Non-AKI [n (%)]	ICPi-AKI [n (%)]	Mortality in AKI [n (%)]	Mortality in non-AKI [n (%)]	AKI Stage 1; 2; 3 [n (%)]	Recovered AKI patients' outcome [n (%)]	Not recovered AKI and outcome (death, need of dialysis, etc.) [n (%)]
Cortazar et al. [20] 2020, North America	276 (67)	138 (33)	67 (48.5)	NA	Stage 2, 59 (43); Stage 3, 79 (57)	FR: 54 (40); PR: 63 (45)	NR: 21 (15); death/NR: 15 (71.4)
García-Carro et al. [24] 2022, Europe	641 (84)	118 (16)	82 (69.5)	315 (49.1)	Stage 1, 69 (58.5); Stage 2 or 3, 49 (41.5)	FR: 38 (32)	Death: 82 (20)
Gupta et al. [19] 2021, North America/Europe/Asia	429 (50)	429 (50)	168 (39.2)	NA	Stage 1, 77 (18); Stage 2, 144 (33.6); Stage 3, 208 (48.5)	OR: 276 (64.3)	Death: 168 (39.2)
	Non-AKI [n (%)]	ICPi-AKI [n (%)]	Total mortality	Mortality in non-AKI [n (%)]	AKI Stage 1; 2; 3 [n (%)]	Recovered AKI patients' outcome [n (%)]	Not recovered AKI and outcome (death, need of dialysis, etc.) [n (%)]
Koks et al. [23] 2021, Europe	644 (95)	32 (5)	314 (46.4)		Stage 1, 26 (81.3); Stage 2, 6 (18.8); Stage 3, 0 (0)	OR: 19 (59.4)	NR: 13 (40.6)
Meraz-Muñoz et al. [21] 2020, North America	297 (96)	12 (4)	Total mortality: 222 (72%)		(NOT only ICPi induced); Stage 1, 27 (53); Stage 2, 11 (22); Stage 3, 13 (25)	FR: 5 (41.6); PR: 5 (41.6)	NR: 2 (16.7)
Seethapathy et al. [22] 2020, North America	594 (99)	5 (1)	1 (20)	NA	Stage 1, 1 (20); Stage 2, 3 (60); Stage 3, 1 (20)	FR: 2 (40); PR: 1 (20)	NR: 2 (40); death/NR: 1 (50)
Shimamura et al. [18] 2021, Asia	125 (82)	27 (18)	17 (63)	68 (54)	Stage 1, 17 (63); Stage 2, 8 (30); Stage 3, 2 (7)	FR: 19 (73)	NR: 8 (27)

NA, not applicable; ICPi-AKI, immune checkpoint inhibitor–induced acute kidney injury; FR, fully recovered; PR, partially recovered; OR, overall recovery of patients in the study; NR, non recovered
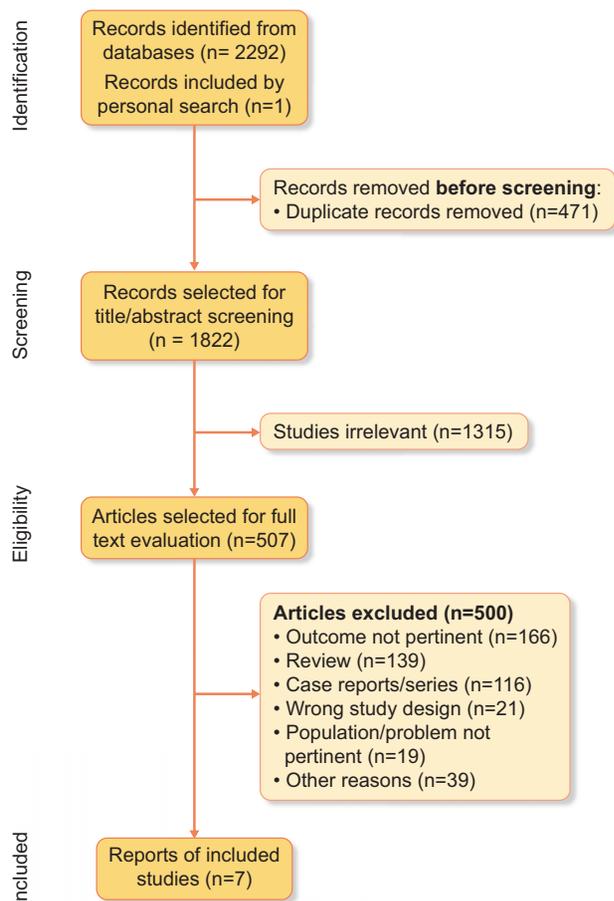
Figure 1: Flow diagram of the study selection process.

without malignancies, patients not receiving ICPi, no reported AKI, AKI patients with not reported outcomes or patients <18 years of age were excluded.

Quality assessment

Quality assessment of the studies included in the meta-analyses was assessed according to the Newcastle-Ottawa Scale, which uses the selection of study groups, assessment of outcomes, and comparability of the groups [16]. According to the Newcastle-Ottawa Scale, a study can earn up to nine stars, representing the highest quality research. The assessment results are demonstrated in Supplementary data, Table S2.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Statistical analysis

Extracted hazard ratios (HR) from the included study protocols were pooled using the random-effects model. We assessed for heterogeneity in the treatment estimates using the CochranQ test and the I^2 statistic (with substantial heterogeneity defined as values >50%) [17]. All statistical analyses were performed using Review Manager (RevMan) Version 5.3 (The Cochrane Collaboration 2012).

RESULTS

Seven studies were included in our final analysis, with a total number of patients of 3767 (895 with AKI and 2872 without AKI), ranging from a minimum of 152 [18] to a maximum of 858 [19]. There were three trials from North America [20–22], two from Europe [23, 24] and one from Asia [18]; the last one included patients from North America, Europe and Asia [19]. The average age of the included patients varied between 61 [21] and 67 years [18]; the proportion of male patients included in the studies was between 50% [22] and 75% [18]. Chronic kidney disease prevalence was between 10.1% [23] and 30% [18]; additionally, hypertension and diabetes were present in 34% [21] to 59.9% [20] and 9.3% [23] to 19% [22], respectively.

Lung cancer was the most frequent neoplasia in five of the studies [18–20, 24, 25], while melanoma was most common in the remaining two [21, 23]. The use of different ICPIs varied between studies: anti CTLA-4 between 1% [18] and 61.9% [21]; anti PD-1 between 25.4% [21] and 91.1% [20]; anti PD-L1 between 5.6% [20] and 27.3% [24]; and combination of ICPIs between 1% [18] and 20.3% [19]. The anti PD-L1 drugs were not used in two studies [21, 23] and Seethapathy *et al.* used only anti PD-1 ICPi [22].

AKI and recovery definition

The KDIGO guideline for AKI definition and staging was employed in all the studies included. Cortazar *et al.* included only patients with at least stage 2 AKI [20]. The incidence of AKI stages 1, 2 and 3 and the need of renal replacement therapy (RRT) varied between 17.9% [19] and 76% [23], 16.7% [23] and 43% [20], 7.3% [23] and 57% [20], and 0% [23] to 9% [20], respectively; two studies did not mention the proportion of AKI stages [22, 24].

Cortazar *et al.* defined complete kidney recovery as serum creatinine <0.35 mg/dL above baseline values and partial recovery serum creatinine >0.35 mg/dL, but less than twice, or liberation from RRT [20]. Full and partial kidney recovery rates were 40% and 45%, respectively [20]. Shimamura *et al.* defined as recovery of the serum creatinine concentration to <0.35 mg/dL above the baseline serum creatinine concentration and recovery rate was 73% [18].

All-cause mortality

Five studies compared the all-cause mortality outcome between patients with and without AKI [18, 21–24]. Overall, the risk of death related to AKI was higher in patients that developed AKI during ICPI treatment [HR 1.42, 95% confidence interval (CI) 1.05–1.92, P = 0.02; heterogeneity $\chi^2 = 11.68$, $I^2 = 66\%$, P = 0.02] (Fig. 2). Two studies analyzed the association of severity of AKI with all-cause mortality [19, 20]. Overall, there was only a trend to a better survival in those with less severe AKI (HR 1.35, 95% CI 0.99–1.83, P = 0.05; heterogeneity $\chi^2 = 0.11$, $I^2 = 0\%$, P = 0.74) (Fig. 3). Finally, there were two studies that evaluated the association of recovery from the AKI episode with survival [18, 20]. Overall, those patients with persistent kidney dysfunction (non-recovery) had an increased risk for all-cause mortality (HR 2.93, 95% CI 1.41–6.08, P = 0.004; heterogeneity $\chi^2 = 0.53$, $I^2 = 0\%$, P = 0.47) (Fig. 4).
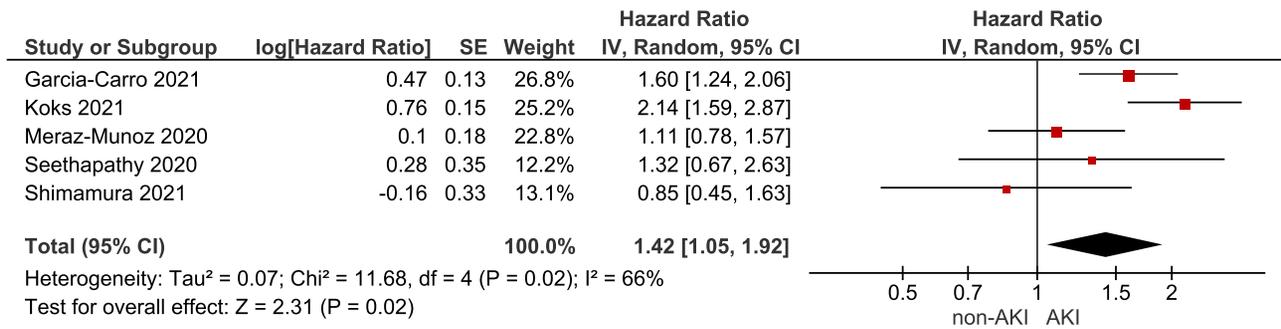
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Garcia-Carro 2021	0.47	0.13	26.8%	1.60 [1.24, 2.06]
Koks 2021	0.76	0.15	25.2%	2.14 [1.59, 2.87]
Meraz-Munoz 2020	0.1	0.18	22.8%	1.11 [0.78, 1.57]
Seethapathy 2020	0.28	0.35	12.2%	1.32 [0.67, 2.63]
Shimamura 2021	-0.16	0.33	13.1%	0.85 [0.45, 1.63]
Total (95% CI)			**100.0%**	**1.42 [1.05, 1.92]**

Heterogeneity: Tau² = 0.07; Chi² = 11.68, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 2.31 (P = 0.02)

Figure 2: Forest plot of association between outcomes of AKI and non-AKI in patients on ICPI.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
4.1.1 Stage 3 vs. Stage 2				
Cortazar 2020	0.21	0.31	25.2%	1.23 [0.67, 2.27]
Subtotal (95% CI)			**25.2%**	**1.23 [0.67, 2.27]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.68 (P = 0.50)				
4.1.2 Stage 3 vs. Stage 1 and 2				
Gupta 2021	0.33	0.18	74.8%	1.39 [0.98, 1.98]
Subtotal (95% CI)			**74.8%**	**1.39 [0.98, 1.98]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.83 (P = 0.07)				
Total (95% CI)			**100.0%**	**1.35 [0.99, 1.83]**

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%

Figure 3: Forest plot of association between Stage 1, 2 AKI and Stage 3 AKI in patients on ICPI.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Cortazar 2020	0.99	0.39	91.4%	2.69 [1.25, 5.78]	2020
Shimamura 2021	1.96	1.27	8.6%	7.10 [0.59, 85.55]	2021
Total (95% CI)			**100.0%**	**2.93 [1.41, 6.08]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
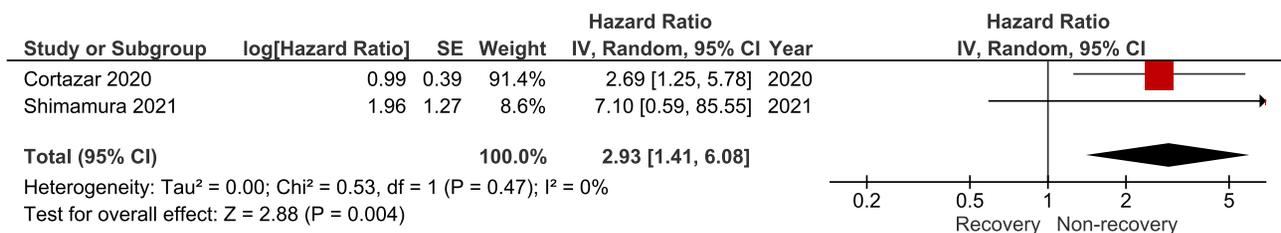Test for overall effect: Z = 2.88 (P = 0.004)

Figure 4: Forest plot of association between recovery and non-recovery of AKI patients in patients on ICPI.

DISCUSSION

Our meta-analysis including seven studies with a total of 3767 patients demonstrates that ICPI-associated AKI is of mild to moderate severity in most cases. The results of our meta-analysis demonstrate high rates of AKI, with incidence rates up to 76% for stage 1 AKI and lower incidence rates for higher stages and for the requirement of RRT. Despite considerable discrepancies among individual studies included in this systematic review, the presence and severity of AKI has an impact on all-cause mortality. Additionally, persistence of AKI further worsens the prognosis. Even though these results are not definitive, they empha-size the need for clear management guidelines for AKI during the course of immune checkpoint inhibitor therapy. Moreover, the early recognition and proper management may improve the clinical outcome.

Another meta-analysis including 13 studies and investigating the association between AKI and PD-1 inhibitors demonstrated a statistically significant higher risk for AKI in patients receiving PD-1 inhibitors compared with non-nephrotoxic controls (relative risk 4.19, 95% CI 1.57–11.18). However, this meta-analysis did not investigate the long-term impact of ICPI-associated AKI on outcomes such as recovery from AKI or all-cause mortality [26].
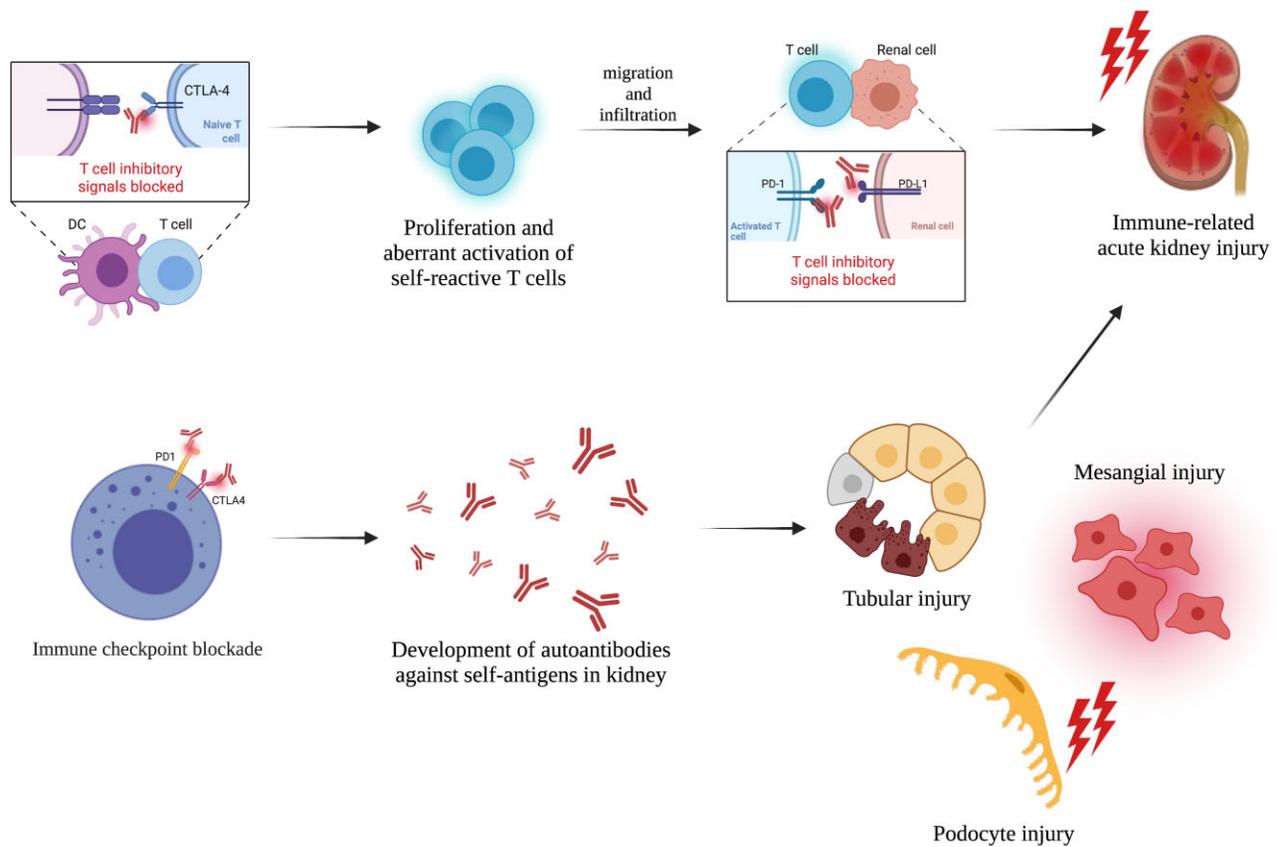
Figure 5: Pathways of AKI development. Blockage of inhibitory pathways allows aberrant T-cell response against self-tissues. Checkpoint blockage also leads to development of autoantibodies and causes damage via several mechanisms. DC, dendritic cells.

Even though studies investigating the exact cause and type of ICPI-associated AKI are limited in number and in extent with lack of adequate biopsy-proven diagnosis, acute tubulointerstitial nephritis appears to be the most common clinical entity which is closer to the entity observed in autoimmune diseases rather than drug-hypersensitivity reactions [27–30]. Such conditions are hypothesized to be caused by ICP-activated T-cells which secrete pro-inflammatory cytokines, and results in loss of tolerance against self-antigens which may result in off-target effects [31]. Other biopsy-proven lesions include granulomas, minimal change disease and thrombotic microangiopathy (Fig. 5) [32, 33]. Management includes temporary or permanent discontinuation of ICPI therapy, supportive therapy and immunosuppressive therapy with intravenous corticosteroids [34].

Major limitations of our meta-analysis include the low number of large-scale prospective cohort studies, variations in the definition of AKI and persistent renal dysfunction across individual studies, and the absence of randomized controlled trials investigating the renal outcomes of immunotherapy in cancer patients which lead to a decline in the power of the meta-analysis. Additionally, variations among the individual studies including the type of malignancy, stage of the disease, comorbidities of the patients involved in those studies, choice for immunotherapeutic medication and basic demographics limit the reproducibility of the results in future studies. Furthermore, the studies included in this meta-analysis, in most cases, do not include the potential confounding conditions that may result in

AKI in cancer patients such as volume depletion (prerenal AKI), use of other potentially nephrotoxic medications and infections that may cause AKI. Similarly, in some studies, the diagnosis of AKI is based on the KDIGO guidelines, while biopsy-proven results, which could illustrate the non-immunotherapy related etiologies for AKI in those patients, are lacking. Lack of a nephrologist in the diagnosis and treatment process in most of the included studies further raises the suspicion for other underlying etiologies. Lastly, our meta-analysis study is unable to reach for a definitive conclusion regarding the effect of AKI stage on mortality due to limited number of studies and variations between studies.

On the other hand, this systematic review and meta-analysis is crucial since it is among the first meta-analysis studies [26, 35] investigating the association between ICPI therapy and kidney injury and its association with clinical outcome such as need for persistence of kidney dysfunction and all-cause mortality. Moreover, these results implicate the need for a clearer management guideline for patients developing AKI during the course of therapy.

In conclusion, the development of AKI in cancer patients receiving ICPIs is an important complication with a potential to increase patient mortality. Therefore, future large-scale randomized studies investigating the incidence of AKI in cancer patients receiving ICPIs along with therapeutic alternatives and the effect of AKI on clinical prognosis are needed for better understanding of this issue.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

FUNDING

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

M.K. is member of the *CKJ* editorial board. A.O. is the previous *CKJ* Editor-in-Chief. The other authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

M.K., S.C., A.B.Y., M.B., R.P., N.B.H. and D.S. contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. M.K., D.S., A.O. and M.A.P. drafted the work or revised it critically for important intellectual content.

(See related article by García-Carro et al. Revisiting the role of acute kidney injury in patients on immune checkpoint inhibitors: a good prognosis renal event with a significant impact on survival. *Clin Kidney J* (2023) 16: 773–775.)

REFERENCES

1. Helmy KY, Patel SA, Nahas GR *et al*. Cancer immunotherapy: accomplishments to date and future promise. *Ther Deliv* 2013;**4**:1307–20. https://doi.org/10.4155/tde.13.88
2. Abbott M, Ustoyev Y. Cancer and the immune system: the history and background of immunotherapy. *Semin Oncol Nurs* 2019;**35**:150923. https://doi.org/10.1016/j.soncn.2019.08.002
3. Perazella MA, Shirali AC. Immune checkpoint inhibitor nephrotoxicity: what do we know and what should we do? *Kidney Int* 2020;**97**:62–74. https://doi.org/10.1016/j.kint.2019.07.022
4. Akhbariyoon H, Azizpour Y, Esfahani MF *et al*. Immune checkpoint inhibition for the treatment of cancers: an update and critical review of ongoing clinical trials. *Clin Immunol* 2021;**232**:108873. https://doi.org/10.1016/j.clim.2021.108873
5. Singh S, Hassan D, Aldawsari HM *et al*. Immune checkpoint inhibitors: a promising anticancer therapy. *Drug Discov Today* 2020;**25**:223–9. https://doi.org/10.1016/j.drudis.2019.11.003
6. Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. *Annu Rev Pathol* 2021;**16**:223–49. https://doi.org/10.1146/annurev-pathol-042020-042741
7. Geisler AN, Phillips GS, Barrios DM *et al*. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol* 2020;**83**:1255–68. https://doi.org/10.1016/j.jaad.2020.03.132
8. Franzin R, Netti GS, Spadaccino F *et al*. The use of immune checkpoint inhibitors in oncology and the occurrence of AKI: where do we stand? *Front Immunol* 2020;**11**:574271. https://doi.org/10.3389/fimmu.2020.574271
9. von Itzstein MS, Khan S, Gerber DE. Investigational biomarkers for checkpoint inhibitor immune-related adverse event prediction and diagnosis. *Clin Chem* 2020;**66**: 779–93.
10. Chauvet S, Courbebaisse M, Ronco P *et al*. Pemetrexed-induced acute kidney injury leading to chronic kidney disease. *Clin Nephrol* 2014;**82**:402–6. https://doi.org/10.5414/CN107921
11. Khalili H, Bairami S, Kargar M. Antibiotics induced acute kidney injury: incidence, risk factors, onset time and outcome. *Acta Med Iran* 2013;**51**:871–8.
12. Krishnan N, Perazella MA. Drug-induced acute interstitial nephritis: pathology, pathogenesis, and treatment. *Iran J Kidney Dis* 2015;**9**:3–13.
13. McDonough PG. Quorum guidelines for meta-analyses. *Fertil Steril* 2003;**80**:228. https://doi.org/10.1016/S0015-0282(03)00583-1
14. Moher D, Liberati A, Tetzlaff J *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535. https://doi.org/10.1136/bmj.b2535
15. Brooke BS, Schwartz TA, Pawlik TM. MOOSE reporting guidelines for meta-analyses of observational studies. *JAMA Surgery* 2021;**156**:787–8. https://doi.org/10.1001/jamasurg.2021.0522
16. Peterson J, Welch V, Losos M *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa: Ottawa Hospital Research Institute* 2011;1–12. http://www.evidencebasedpublichealth.de/download/Newcastle_Ottowa_Scale_Pope_Bruce.pdf
17. Higgins JP, Thompson SG, Deeks JJ *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60. https://doi.org/10.1136/bmj.327.7414.557
18. Shimamura Y, Watanabe S, Maeda T *et al*. Incidence and risk factors of acute kidney injury, and its effect on mortality among japanese patients receiving immune check point inhibitors: a single-center observational study. *Clin Exp Nephrol* 2021;**25**:479–87. https://doi.org/10.1007/s10157-020-02008-1
19. Gupta S, Short SA, Sise ME *et al*. Acute kidney injury in patients treated with immune checkpoint inhibitors. *J Immunother Cancer* 2021;**9**:e003467. https://doi.org/10.1136/jitc-2021-003467
20. Cortazar FB, Kibbelaar ZA, Glezerman IG *et al*. Clinical features and outcomes of immune checkpoint inhibitor–associated AKI: a multicenter study. *J Am Soc Nephrol* 2020;**31**:435–46. https://doi.org/10.1681/ASN.2019070676
21. Meraz-Muñoz A, Amir E, Ng P *et al*. Acute kidney injury associated with immune checkpoint inhibitor therapy: incidence, risk factors and outcomes. *J Immunother Cancer* 2020;**8**:e000467.
22. Seethapathy H, Zhao S, Strohbehn IA *et al*. Incidence and clinical features of immune-related acute kidney injury in patients receiving programmed cell death ligand-1 inhibitors. *Kidney Int Rep* 2020;**5**:1700–5. https://doi.org/10.1016/j.ekir.2020.07.011
23. Koks MS, Ocak G, Suelmann BB *et al*. Immune checkpoint inhibitor-associated acute kidney injury and mortality: an observational study. *PLoS One* 2021;**16**:e0252978. https://doi.org/10.1371/journal.pone.0252978
24. García-Carro C, Bolufer M, Bury R *et al*. Acute kidney injury as a risk factor for mortality in oncological patients receiving

checkpoint inhibitors. *Nephrol Dial Transplant* 2022;**37**:887–94. doi: 10.1093/ndt/gfab034

25. Seethapathy H, Zhao S, Chute DF *et al*. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. *Clin J Am Soc Nephrol* 2019;**14**:1692–700. https://doi.org/10.2215/CJN.00990119

26. Manohar S, Kompotiatis P, Thongprayoon C *et al*. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis. *Nephrol Dial Transplant* 2019;**34**:108–17. https://doi.org/10.1093/ndt/gfy105

27. Cortazar FB, Marrone KA, Troxell ML *et al*. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int* 2016;**90**:638–47. https://doi.org/10.1016/j.kint.2016.04.008

28. Mamlouk O, Selamet U, Machado S *et al*. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. *J Immunother Cancer* 2019;**7**:2. https://doi.org/10.1186/s40425-018-0478-8

29. Marco T, Anna P, Annalisa T *et al*. The mechanisms of acute interstitial nephritis in the era of immune checkpoint inhibitors in melanoma. *Ther Adv Med Oncol* 2019;**11**:1758835919875549.

30. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. *Am J Kidney Dis* 2016;**68**:287–91. https://doi.org/10.1053/j.ajkd.2016.02.057

31. Franzin R, Netti GS, Spadaccino F *et al*. The use of immune checkpoint inhibitors in oncology and the occurrence of AKI: where do we stand? *Front Immunol* 2020;**11**:574271. https://doi.org/10.3389/fimmu.2020.574271

32. Kidd JM, Gizaw AB. Ipilimumab-associated minimal-change disease. *Kidney Int* 2016;**89**:720. https://doi.org/10.1016/j.kint.2015.11.028

33. Izzedine H, Gueutin V, Gharbi C *et al*. Kidney injuries related to ipilimumab. *Invest New Drugs* 2014;**32**:769–73. https://doi.org/10.1007/s10637-014-0092-7

34. Herrmann SM, Perazella MA. Immune checkpoint inhibitors and immune-related adverse renal events. *Kidney Int Rep* 2020;**5**:1139–48. https://doi.org/10.1016/j.ekir.2020.04.018

35. Li H, Xu J, Bai Y *et al*. Nephrotoxicity in patients with solid tumors treated with anti-PD-1/PD-L1 monoclonal antibodies: a systematic review and meta-analysis. *Invest New Drugs* 2021;**39**:860–70. https://doi.org/10.1007/s10637-020-01039-5