Evaluating short and long-term renal outcomes in patients who develop drug-associated acute kidney injury

Kangho Suh, PharmD, PhD[1], Jingye Yang, MS[1], Nabihah Amatullah, PharmD[1], Sandra Kane-Gill, PharmD, MSc[1]
[1]Department of Pharmacy & Therapeutics, University of Pittsburgh

BACKGROUND

- Acute kidney injury (AKI) frequently occurs in the hospital setting, with an incidence up to 22%.[1,2]
- AKI results in both short- and long-term complications including longer hospital length-of-stay, need for renal replacement therapy, an increased risk of progression to chronic kidney disease (CKD), reduced health-related quality of life, and significantly increased long-term mortality.[3,4]
- Around 30% of AKI in hospitalized patients is caused by nephrotoxic drugs with the notion being drug-associated AKI (D-AKI) has a greater likelihood of favorable short and long-term outcomes since the toxicity source can be managed or discontinued.[5,6]
- Whether patients with D-AKI fare better in the real world compared to non D-AKI is not well established.

OBJECTIVE

- Our objective was to compare post-discharge major adverse kidney events (MAKE) between D-AKI and non D-AKI patients at 30 (MAKE30) and 90 (MAKE90) days for critically ill patients.

METHODS

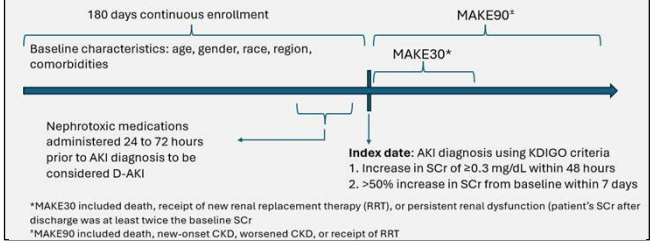
Data Source

- We used a large integrated electronic health record (EHR) and administrative claims database from the year 2011 to 2020.

Study Design

- Retrospective cohort study (Figure 1)
- SCr values from the EHR were used to identify baseline SCr in the following order:
  1) median SCr taken from a time period of 180 days prior to 7 days prior of hospital visit
  2) admission SCr taken from within the first 24 hours of admission
  3) calculation-based SCr based on the Modification of Diet in Renal Disease (MDRD) equation using age and gender

Figure 1. Study Design



*MAKE30 included death, receipt of new renal replacement therapy (RRT), or persistent renal dysfunction (patient's SCr after discharge was at least twice the baseline SCr
±MAKE90 included death, new-onset CKD, worsened CKD, or receipt of RRT

METHODS

D-AKI identification and AKI staging

- Drugs that were determined to have a nephrotoxic potential higher than "probable" from a modified Delphi panel of nephrology experts were used to determine patients with D-AKI in the critical care setting (Table 1).[7]

Data Analysis

- Propensity scores and greedy matching were used to control for observed confounding based on demographic and clinical characteristics (Table 1).
- Cox proportional hazard models were used to compare MAKE30 and MAKE90 between patients with D-AKI and non D-AKI.

Table 1. Drugs that were used to identify drug-associated AKI

Nephrotoxic potential probable with route use			
Ibuprofen	Ketoprofen	Rofecoxib	Tacrolimus
Nephrotoxic potential probable to definite			
Amikacin	Amphotericin B	Carboplatin	Cidofovir
Cisplatin	Colistin	Cyclosporine	Diclofenac sodium
Gentamicin	Indomethacin	Ketorolac	Methotrexate
Naproxen	Tobramycin	Vancomycin	Foscarnet

RESULTS

Table 2. Baseline Characteristics

	Non D-AKI (n=574)	D-AKI (n=574)	SMD
Age, n (%)			0.08
18 to 45	47 (8.19)	51 (8.89)	
45 to 55	50 (8.71)	62 (10.80)	
55 to 65	130 (22.65)	147 (25.61)	
>65	347 (60.45)	314 (54.70)	
Female, n (%)	213 (37.11)	226 (39.37)	0.09
Race, n (%)			0.11
White	524 (91.29)	494 (86.06)	
Black	45 (7.84)	72 (12.54)	
Other	5 (0.87)	8 (1.39)	
Region, n (%)			0.12
Midwest	255 (44.43)	307 (53.48)	
Northeast	94 (16.38)	72 (12.54)	
South	177 (30.84)	159 (27.70)	
West	48 (8.36)	36 (6.27)	
Congestive heart failure	79 (13.76)	72 (12.54)	0.04
Cardiac arrhythmia	109 (18.99)	108 (18.82)	0.00
Valvular disease	117 (20.38)	81 (14.11)	0.17
Peripheral vascular disorders	64 (11.15)	60 (10.45)	0.02
Chronic pulmonary disease	113 (19.69)	104 (18.12)	0.04
Hypothyroidism	37 (6.45)	40 (6.97)	0.02
Fluid and electrolyte disorders	54 (9.41)	62 (10.80)	0.02
Depression	50 (8.71)	40 (6.97)	0.06
Cancer	44 (7.67)	46 (8.01)	0.01
Diabetes	84 (14.63)	95 (16.55)	0.05
Hypertension	193 (33.62)	201 (35.02)	0.03

RESULTS

- After propensity score matching, 574 patients in each cohort were included (Table 2).
- Patient characteristics were relatively well-balanced between the two groups.
- Patients with D-AKI had a 26% and 24% higher risk of MAKE30 and MAKE90, respectively, compared to patients with non D-AKI (Tables 3 and 4).

Table 3. Risk of MAKE30

	Non D-AKI (n=574)	D-AKI (n=574)
MAKE30, n (%)	151 (26.31)	181 (31.53)
Person-months	494	476
Crude incidence rate per 100 person-months	30.57	38.03
Adjusted hazard ratio	1.26 (95% CI: 1.01, 1.58)	

Table 4. Risk of MAKE90

	Non D-AKI (n=574)	D-AKI (n=574)
MAKE90, n (%)	166 (28.92)	195 (33.97)
Person-months	1,276	1,211
Crude incidence rate per 100 person-months	13.01	16.10
Adjusted hazard ratio	1.24 (95% CI: 1.00, 1.54)	

CONCLUSIONS

- To the best of our knowledge, this is the first assessment comparing MAKE30 and MAKE90 in patients with D-AKI vs. non D-AKI in the critical care setting using a large nationally represented database
- The higher risk of MAKE30 and MAKE90 in D-AKI patients went against conventional thought that these patients would fare better given that the likely cause of their AKI could be dose adjusted or stopped.
- Further research is needed to determine the mechanisms behind our findings.

Strengths

- We used SCr to diagnose AKI whereas other studies in the literature used less precise ICD-9 and 10 codes, which are not specific for AKI.
- We were specific as to the temporality of drugs administered and diagnosis of D-AKI whereas other studies claimed D-AKI even when the potential nephrotoxic drug was administered after AKI diagnosis.

Limitations

- While we categorized D-AKI based on an expert panel, the nephrotoxic potential of each drug was not robustly assessed through randomized controlled trials.

References
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