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Clinical Characteristics and Outcomes of Drug-Induced Acute Kidney Injury Cases

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Clinical Characteristics and Outcomes of Drug-Induced Acute Kidney Injury Cases

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Abstract

Introduction: Drug-induced acute kidney injury (DI-AKI) is a frequent adverse event. The identification of DI-AKI is challenged by competing etiologies, clinical heterogeneity among patients, and a lack of accurate diagnostic tools. Our research aims to describe the clinical characteristics and predictive variables of DI-AKI.

Methods: We analyzed data from the DIRECT study (NCT02159209), an international, multi-center, observational cohort study of enriched clinically adjudicated DI-AKI cases. Cases met the primary inclusion criteria if the patient was exposed to at least one nephrotoxic drug for a minimum of 24 hours prior to acute kidney injury (AKI) onset. Cases were clinically adjudicated and inter-rater reliability (IRR) was measured using Krippendorff's alpha. Variables associated with DI-AKI were identified using L1 regularized multivariable logistic regression. Model performance was assessed using the area under the receiver operating characteristic curve (ROC AUC).

Results: 314 AKI cases met the eligibility criteria for this analysis, and 271 (86%) cases were adjudicated as DI-AKI. The majority of the AKI cases were recruited from the United States (68%). The most frequent causal nephrotoxic drugs were vancomycin (48.7%), non-steroidal anti-inflammatory drugs (18.2%), and piperacillin/tazobactam (17.8%). The IRR for DI-AKI adjudication was 0.309. The multivariable model identified age, vascular capacity, hyperglycemia, infections, pyuria, serum creatinine trends, and contrast media as significant predictors of DI-AKI with good performance, ROC AUC 0.86.

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Conclusions: The identification of DI-AKI is challenging even with comprehensive

adjudication by experienced nephrologists. Our analysis identified key clinical

characteristics and outcomes of DI-AKI compared to other AKI etiologies.

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Introduction

Drug-induced acute kidney injury (DI-AKI) is a common adverse drug event (ADE) affecting approximately 14-26% of the hospitalized adult population.[1,2,3,4] Hospitalized patients, particularly critically ill patients, are often exposed to numerous nephrotoxic drugs, and the risk of AKI has been shown to increase by 53% for each nephrotoxic drug exposure.[5] When a patient experiences AKI, clinicians must evaluate concomitant risk factors and the nephrotoxic risk profile for each drug exposure based on published literature to determine causality for each exposure and discontinue causal drugs where feasible.[2] This is challenging given current gaps in the literature, which include variable definitions of DI-AKI employed in studies, lack of diagnostic markers of drug-specific injury, and few published studies on AKI sub-phenotypes.[6,7] Clinical manifestations and the onset of DI-AKI vary by drug and can be overlooked with short-term drug exposures. There is significant clinical heterogeneity among patients, and consequently, it is very challenging to determine the role of drugs amidst other etiologies of AKI, such as sepsis or hypotension. Causality assessment tools for ADEs have been shown to perform well for general ADEs, with some limitations.[8,9,10] These tools have not been validated for DI-AKI, which requires a careful evaluation of competing clinical risk factors and concurrent nephrotoxin exposures by an experienced clinician.[11]

The study aims were to (1) describe the injury, risk factors, and outcomes of DI-AKI, and (2) identify the best predictive variables that differentiate high probability DI-AKI cases from other etiologies of AKI in inpatient settings in a well-characterized cohort of adult patients with clinically adjudicated hospital-acquired DI-AKI.

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Methods

Study Populations, Eligibility Criteria, and Data Collection

In this study, we retrospectively analyzed data from hospitalized adult patients, aged 18 years or order, enrolled in the Drug-Induced Renal Injury Consortium (DIRECT) study (NCT02159209), which was conducted during the period from February 2013 to December 2015.[12] We refer the reader to the DIRECT study methodology which has been published previously.[12] In summary, DIRECT is an international, multi-center, observational cohort study of enriched DI-AKI cases that underwent clinical adjudication. The study was approved by the institutional research board for human subjects at the coordinating center, and subjects provided informed consent. Each of the 42 participating centers was required to follow institutional requirements for human subject research approval and informed consent.

Suspected DI-AKI cases identified by the principal investigator at each participating site were electronically screened for eligibility, enrolled by the site, and underwent clinical adjudication. Eligible cases included subjects who experienced AKI stage 2 or higher during their hospitalization, defined as a doubling in serum creatinine (SCr) from baseline after exposure to candidate nephrotoxic drug(s) for a minimum of 24 hours (Supplemental Table S.1). AKI was staged according to 2012 Kidney Disease Improving Global Outcomes (KDIGO) criteria using the peak to baseline SCr ratio.[13] Baseline SCr was defined as the lowest SCr within 90 days before drug exposure. In patients who presented without baseline SCr, nadir SCr during hospitalization was used to back-calculate baseline SCr. Cases were excluded if the patients had

undergone kidney or bone marrow transplants, had chronic kidney disease (CKD) stage 5, had exposure to more than three possible causal drugs, or had incomplete patient information on the time course of drug exposure. For this analysis, we excluded patients who presented to the hospital with AKI or those ~~enrolled in the DIRECT study~~with biopsy proven glomerular ~~phenotype~~ injury (Figure 1).[11]

Data was collected at pre-defined time points based on causal drug exposure and course of injury, including hospital admission, pre-drug exposure, start of drug exposure, onset of AKI, peak SCr, drug discontinuation or dosage adjustment, nadir SCr, hospital discharge, 28- and 90-days post-injury. Data elements collected included vital signs, laboratory results, urine studies, physical examination, AKI risk factors, kidney replacement therapy (KRT), and survival status (Table 1). Definitions of AKI risk factors were provided to site investigators. For example, increased vascular capacity was defined as clinical events leading to reduced blood perfusion to the kidney (e.g., mean arterial pressure < 65 mmHg, sepsis). Hyperglycemia was defined as blood sugar > 110 mg/dL or patient was on insulin. In this analysis, AKI risk factors were present if they were recorded in the 72 hours preceding AKI onset. Urinalysis findings were defined as: minimal (< 1+), moderate (1+ to 2+), and heavy (> 2+) for protein and glucose in the urine. Positive urinary sediment findings were defined as minimal (< 6), moderate (6-20), and heavy (> 20) for white and red blood cells, presence of either hyaline, granular, cellular hemoglobin, fatty, waxy, tubular, or broad casts.

Structured data elements were extracted electronically from the electronic health record (EHR) where feasible, while unstructured data was collected manually. All data was de-identified and populated in electronic case report forms stored in a web-based

database. A web platform was developed, allowing the adjudicators to evaluate the clinical data elements across study timepoint and perform clinical adjudication (Supplemental Figure S.1).

Clinical Adjudication

All cases enrolled in the DIRECT study underwent clinical adjudication by a panel of 9 nephrologists and one pharmacist. All cases were reviewed by the pharmacist (LA) to ensure complete and accurate data prior to adjudication by two independent nephrologists (EM, DC, JC, RC, AL, SG, MZ, DS) as DI-AKI vs. Not DI-AKI. If an unanimous agreement between the two adjudicators was not achieved, a third adjudicator (RM) was introduced to resolve the tie and achieve an agreement. None of the adjudicators were involved with the clinical care of the cases they adjudicated.

Each case was summarized by visually displaying SCr graphs with drug exposure dates overlayed and a summary of AKI risk factors and clinical findings at each timepoint including but not limited to vital signs, laboratory values, procedures, contrast exposure, drug doses and drug concentrations (Supplemental Figure S.1). To standardize the adjudication process and assure the reproducibility of findings, adjudicators were provided with a list of candidate nephrotoxic drugs (Supplemental Table S.1) and were trained on the adjudication process which included completing two causality assessment tools, Naranjo Probability Scale (NPS) (Supplemental Figure S.2) and Liverpool Probability Scale (LPS) (Supplemental Figure S.3) for each candidate nephrotoxic drug.[9,10] Using the causality scores and reviewing the case

summary, adjudicators completed the Adjudicator Probability Scale (APS) using a web-based rubric to determine the contribution of candidate nephrotoxic drugs and concomitant risk factors for AKI (Supplemental Figure S.4). NPS is a questionnaire tool that involves ten 'Yes', 'No', or 'Unknown' questions. The AE rating is determined based on the total score as 'Definite' (≥ 9), 'Likely' (5-8), 'Possible' (1–4), 'Unlikely' (≤ 0) (Supplemental Figure S.2). LPS is a decision tree flowchart to establish an AE probability rating of 'Definite', 'Probable', 'Possible', or 'Unlikely' (Supplemental Figure S.3). Guided by the NPS and LPS, adjudicators completed the APS for each case. APS is comprised of 'Definite', 'Probable', 'Possible', or 'Unlikely' probability rating for nephrotoxic drugs and concomitant risk factors. For example, in the case of a patient who developed AKI after treatment with gentamicin and ibuprofen, the clinical adjudicator may determine that gentamicin was a 'Definite' cause and ibuprofen and underlying and concomitant risk factors were 'Unlikely' causes of AKI. Finally, each case was adjudicated as DI-AKI vs. Not DI-AKI by adjudicators.

Descriptive Statistical Analysis and Inter-Rater Reliability

Cases were grouped into DI-AKI or Not DI-AKI, and we summarized the patient demographics, risk factors, and outcomes using descriptive statistics such as mean (standard deviation [SD]) or median (inter-quartile range [IQR]) or counts (%), where appropriate. Continuous variables were analyzed by two independent samples t-test or the Wilcoxon rank-sum test, as appropriate. Categorical variables were analyzed by chi-square test or Fisher's exact test, as appropriate. We measured the inter-rater reliability (IRR) of DI-AKI adjudication (DI-AKI vs. Not DI-AKI) between the two primary adjudicators across all cases using Krippendorff's alpha statistic (ka). Krippendorff's

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alpha is a reliability coefficient developed to measure the agreement among adjudicators. Unlike other IRR measures, Krippendorff's alpha can be applied to any number of adjudicators, not only two. Additionally, it can handle small sample sizes and missing data.[14]

Multivariable Analysis of DI-AKI

We examined 166 clinical variables from the DIRECT study and grouped variables under the following domains: demographics (3), past medical history (25), pre-admission medications (5), psychosocial (2), AKI risk factors (15), physical examination (17), vitals (9), trends - vitals (6), labs (25), trends – labs (18), urinalysis (20), contrast exposure (4), urine chemistry (10), kidney biopsy (4), hemodialysis and critical illness (3).

Given the critical role of SCr trends and temporal relationship to drug exposure,[2] we developed a set of variables to capture the relative change in SCr across several time points of the study (Supplemental Table S.2) using the following formula:

$$SCr\ Change\ = \frac{SCr_{final} - SCr_{initial}}{SCr_{initial}} \times 100\%$$

To evaluate the relationship between contrast agent exposure and AKI, we developed two variables: (1) contrast volume (mL) administered between hospital admission up to AKI onset; (2) number of days between contrast exposure date and AKI onset. For subjects with multiple exposures, we considered the exposure closest to AKI onset.[15,16]

When constructing the multivariable model, we aimed to identify a

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parsimonious set of predictors that best distinguish DI-AKI cases from other etiologies of AKI. To achieve that, we employed a staged approach to variable selection. First, we eliminated variables that met the following criteria: (1) past medical history variables with < 2% prevalence; (2) laboratory variables with > 30% missing except for blood eosinophil count; (3) urinalysis variables with > 30% missing except for urinary sediments; (4) urine chemistry variables with > 30% missing except for creatinine and protein. Continuous variables were imputed by median value substitution. Categorical variables were imputed by most frequent value substitution. Second, we performed univariable analyses between the remaining variables and the DI-AKI ascertainment outcome, removing predictors with a $P > 0.1$. Finally, we utilized penalized logistic regression using the L1 penalty (Least Absolute Shrinkage and Selection Operator—LASSO) with k-fold cross-validation (k = 10) to select a final subset of the predictor variables.[17]

The final subset of predictors identified by the variable selection procedure described above was used in an unpenalized logistic regression model with DI-AKI as the outcome. We evaluated model discrimination using the area under the receiver operating characteristic curve (ROC AUC), and model calibration with an observed-to-expected calibration plot and the Hosmer–Lemeshow statistic.[18] Confidence intervals (CI) of ROC AUC were generated using bootstrapping (100 bootstrap samples).[19] We assessed the performance of our model's sensitivity and specificity at Youden's index, a commonly used cutoff that attempts to maximize sensitivity and minimize false positives.[20]

Results

Patient Cohort and Clinical Adjudication

In the DIRECT study, 1,212 AKI cases were screened, of which 631 cases underwent clinical adjudication. A total of 314 hospitalized adult cases met the eligibility criteria for this analysis (Figure 1). The majority of cases were from the United States (68%), followed by India (11%), and the United Kingdom (10%), respectively (Supplemental Table S.3). Of the 314 cases, 271 (86%) were adjudicated as DI-AKI with unanimous agreement in 233 (74.2%) cases, corresponding to poor agreement (*ka* 0.309).The proportion of cases requiring a tiebreaker was comparable between the cases clinically adjudicated as DI-AKI and Not DI-AKI (26.1 vs. 21.0%, *P* = 0.55). Assessment of clinical notes from tiebreaker adjudication of Not DI-AKI cases indicated that drug causality could not be established due to concerns related to temporality in relationship to AKI onset, drug exposure (dosing or concentration), or competing AKI risk factors (Supplemental Table S.4).

The cohort demographics are summarized in Table 2. Males represented 51% of the cohort with a median (IQR) age of 55 (31) years. Caucasian patients represented about half of the cohort (55%). The most frequent comorbidities were hypertension (44.6%), diabetes mellitus (30.6%), and CKD (19.4%). Except for diabetes mellitus (33.2 vs. 16.3%, *P* = 0.03), the prevalence of comorbidities was similar between DI-AKI and Not DI-AKI groups. A total of 76 (24.2%) cases developed AKI during their intensive care unit (ICU) stay, of which a larger proportion

was clinically adjudicated as Not DI-AKI compared to DI-AKI (21.4 vs. 41.9%, $P <$ 0.01) (Table 2).

Patients clinically adjudicated as DI-AKI and Not DI-AKI groups were exposed to a comparable mean (SD) number of candidate drugs (1.5 (0.68) vs. 1.4 (0.63), $P =$ 0.24). Vancomycin was the most frequent candidate nephrotoxic drug (48.7%), followed by NSAIDs (18.2%) and piperacillin/tazobactam (17.8%) (Table 2). The proportion of certain candidate causal drugs was significantly different between DI-AKI and Not DI-AKI groups. A greater proportion of clinically adjudicated DI-AKI cases had vancomycin (53.8 vs. 23.3%, $P < 0.01$) and NSAIDs (21.0 vs. 0.0%, $P <$ 0.01) suspected as candidate causal drugs compared to Not DI-AKI cases. While a greater proportion of Not DI-AKI cases had cephalosporins (25.6 vs. 8.5%, P < 0.01) and loop diuretics (16.3 vs. 2.2%, $P < 0.01$) suspected as candidate causal drugs compared to DI-AKI cases. The median vancomycin trough concentration was higher in the cases adjudicated as DI-AKI compared to the cases adjudicated as Not DI-AKI (31.9 vs. 27.6 mcg/dL, $P = 0.43$).

Our evaluation of AKI risk factors revealed that among patients adjudicated as DI-AKI, a lower proportion had undergone cardiac surgery (3.3 vs. 11.3%, $P < 0.01$) and had increased vascular capacity (8.1 vs. 11.6%, $P = 0.03$), and a higher proportion had hyperglycemia (48.3 vs. 30.2%, $P = 0.03$) (Table 3). The proportion of AKI risk factors was comparable between cases that required and did not require a tiebreaker adjudicator (Supplemental Table S.5). A total of 33 patients underwent kidney biopsy, of whom 15 (45%) had histopathology consistent with acute interstitial nephritis (AIN), 8 (24%) with acute tubular necrosis (ATN), and 7 (21%) as mixed

pattern of AIN and ATN (Supplemental Table S.6). Interestingly, all cases with kidney

biopsy results were adjudicated as DI-AKI.

The mean (SD) baseline SCr was not statistically different between DI-AKI

and Not DI-AKI groups 0.91 (0.44) vs. 0.98 (0.81) mg/dL, P = 0.60 and increased to

a maximum of 4.5 (2.7) vs. 3.7 (3.2) mg/dL, P = 0.12 (Table 4). At discharge, the

SCr remained elevated at 2.2 (1.5) vs. 2.1 (1.4) mg/dL, P = 0.72, reflecting the

severity of the injury (Figure 2). A significantly greater proportion of patients clinically

adjudicated as DI-AKI had AKI stage 3 (73.7 vs. 48.8%, P < 0.01). The rate of acute

kidney disease was significantly higher in the DI-AKI group at discharge (61.3 vs

32.6%, P < 0.01), but it was nonsignificant at 28 (27.3 vs. 25.6%, P = 1) and 90-day

(14.8 vs. 11.6%, P = 0.79) follow up.[21] No statistically significant differences

between the groups were observed for the duration from drug exposure to AKI

onset, length of hospital stay, acute kidney disease, need for renal replacement

therapy, and inpatient mortality (Table 4).

Clinical Predictors of DI-AKI Adjudication

A total of 166 clinical variables (Supplemental Table S.7) were summarized,

evaluated, and 28 predictions were chosen by the feature selection process

(Supplemental Table S.8). Table 5 lists the odds ratios (ORs) from the multivariable

logistic model for statistically significant predictors differentiating DI-AKI in

hospitalized adults from other etiologies of AKI. The temporality and pattern of SCr

rise prior to nephrotoxic drug exposure reduced the probability of DI-AKI adjudication.

For every 10% increase in SCr from pre-drug exposure to the start of drug exposure,

DI-AKI adjudication odds were reduced by 43% (OR = 0.57, 95% CI 0.41-0.77). AKI

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risk factors of volume status, such as increased vascular capacity, receipt of red blood cells transfusions and remarkable ascites on physical examination, reduced the odds of DI-AKI as well (Table 5).

Trends of platelets and white blood cell counts affected DI-AKI ascertainment. For every 100 x 10^9/L increase in platelets count from the start of drug exposure to AKI onset, there was a decrease in the odds of DI-AKI adjudication by 60% (OR = 0.40, 95% CI 0.21-0.73). Similarly, for every 5 x 10^9/L increase in white blood cell count from the start of drug exposure to AKI onset, there was a decrease in the odds of DI-AKI adjudication by 36% (OR = 0.64, 95% CI 0.41-0.98). Lastly, an increase in the time duration between exposure to contrast medium and AKI onset increased the odds of DI-AKI adjudication by 8% (OR = 1.08, 95% CI 1.01-1.15) for every additional day (Table 5).

The ROC AUC of the final model was 0.86 (95% CI 0.78 - 0.90). The Hosmer–Lemeshow test was statistically significant (X-squared = 17.16, df = 8, P = 0.02); despite that, the model appeared to have acceptable overall calibration, judged by the smoothed calibration curve with agreement across the range of predicted probabilities (Figure 3).[22] At the Youden's index, the model sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 0.88, 0.84, 0.97, and 0.53, respectively.

Discussion

In the DIRECT study, a well characterized cohort of AKI cases underwent causality assessment and clinical adjudication to differentiate DI-AKI from other etiologies. In this analysis, we summarized the clinical characteristics and outcomes from comprehensive data (i.e., demographics, past medical history, laboratory results, vital signs, and AKI risk factors) of hospitalized adult patients with suspected DI-AKI and generated a statistical model clinical predictors that differentiates clinically adjudicated DI-AKI from other AKI etiologies. Our multivariable model achieved a performance of 0.86 (95% CI 0.78 - 0.90) measured by ROC AUC, demonstrating a comprehensive approach that could improve the recognition of DI-AKI. This analysis was conducted in a multinational cohort of patients, making our findings widely applicable to a range of populations.[23] Our work contributes to the understanding of AKI sub-phenotypes as it relates to drug-induced causes and can enhance future research focused on developing prospective AKI prediction models.[24,25]

Our analysis revealed that most clinical characteristics and risk factors were shared between the DI-AKI and Not DI-AKI groups, attesting to the complexity of establishing a causal relationship between drug exposure and AKI. Treatment with drugs such as vancomycin and NSAIDs was more frequent in the DI-AKI group, reflecting the adjudicator's knowledge of key factors in establishing a causal relationship such as pharmacological mechanisms, epidemiology of DI-AKI, dose-toxicity relationship, utilization, and availability of drug concentrations. In contrast, treatment with loop diuretics and cephalosporin antibiotics was more frequent in the Not DI-AKI group, reflecting adjudicator uncertainty on causality. Although all drugs

included in this analysis have been established as nephrotoxic agents, their relevant contribution to AKI in clinically adjudicated cases is yet to be fully understood, especially in the context of their clinical indications, underlying patient diagnosis, and concomitant AKI risk factors.[26]

AKI adjudication by nephrologists compared to biomarker-based definitions has been evaluated in previous studies with good agreement. However, most studies have focused on establishing the occurrence of AKI rather than adjudication of AKI sub-phenotypes. The lack of standard definitions or consensus criteria for AKI-phenotypes complicates clinical adjudication. In the Tribe-AKI study, Koyner et al. reported poor IRR (Fleiss' kappa 0.046) between clinical adjudicators in differentiating ATN versus prerenal azotemia in patients undergoing cardiac surgery.[27] In the DIRECT study, investigators recruited suspected DI-AKI cases and employed standardized definitions with criteria for phenotypes resulting in a relative improvement in the IRR of clinical adjudication ($ka = 0.309$); despite this, the reliability remained below the significance threshold of 0.677.[14] This demonstrates that AKI ascertainment is consistently a debatable decision, even amongst experienced clinicians. IRR can be improved by using standardized consensus definitions of DI-AKI, capturing the relevant clinical variables for these definitions in a consistent method across sites, and training clinical adjudicators to reduce variability in the adjudication process.[12]

We report certain risk factors associated with the adjudication of DI-AKI cases from other causes of AKI. While certain traditional risk factors of AKI may not be selected by the final multivariable model, it is expected since this analysis aimed to

identify distinctive clinical characteristics of DI-AKI using an enriched cohort, yielding results specific to this unique subset of AKI cases. The following variables made DI-AKI ascertainment less likely: age [11], increased vascular capacity [28], diabetes [29], heavy pyuria [30], and increase in SCr prior to treatment with nephrotoxic drugs.[11] These findings align with our current understanding of AKI etiologies and risk factors. It is worth noting that most variables from the multivariable model were associated with lowering the odds of DI-AKI adjudication. This observation could be attributed to two factors. First, the DIRECT study eligibility criteria aimed to select DI-AKI cases by recruiting patients exposed to nephrotoxic drugs before AKI onset.[12] This resulted in the absence of traditional variables associated with establishing the ADE. Second, there is a scarcity of biomarkers and well-established clinical criteria specific to DI-AKI, making the diagnosis complex by requiring the evaluation of the contribution of competing etiologies.[7] Thus, the multivariable model results should not be interpreted as causative or protective of DI-AKI, but rather these predictors inform the identification of probable DI-AKI cases.

Kidney biopsy is a valuable tool for determining the pathophysiology of AKI, which helps to inform the causality ascertainment when paired with clinical observations.[31] The rate of biopsy-confirmed AIN cases in this analysis was 66% compared to 5-27% reported in other AKI studies. This is not surprising given the number of antibiotics, NSAID, and proton pump inhibitor cases included in this analysis.[32] While nephrotoxic agents are responsible for 70%-90% of AIN cases, ATN is multifactorial and can be caused by ischemia, sepsis, or nephrotoxins. The rate of biopsy-confirmed ATN varies and can reach up to 50% in cases of severe

sepsis.[32,33] Although kidney biopsy may reveal histopathologic patterns associated with DI-AKI, it is challenging to include its findings in statistical modeling studies due to the limited number of AKI cases with biopsy results.

Our multivariable logistic regression model achieved good performance with a ROC AUC of 0.86 for the outcome of DI-AKI. This finding supports the hypothesis that a probabilistic model can be used to identify DI-AKI cases with good discrimination. The high specificity of 0.84 enables the ruling out of AKI cases that are not induced by exposure to nephrotoxic drugs. The PPV of 0.97 ensures that cases deemed to be DI-AKI by the algorithm are highly probable cases. Probabilistic models allow the user to manipulate the thresholds for varying levels of sensitivity and specificity for defining cohorts in secondary data use analyses. The calibration plot appears relatively uniform, indicating that the agreement between the estimated and observed number of events is consistent across all cases. The variables selected in our model use clinical data often available as structured data in the EHR of patients in the United States and other countries.[34] This significantly improves the utility of our model when used to analyze clinical data extracted from EHR or clinical data repositories.

We note limitations that will require refinement and future investigation. First, this is a retrospective analysis of enriched DI-AKI cases that were selected by DIRECT study principal investigators, explaining the 86% DI-AKI adjudication rate in this study.[1 2] It is not uncommon for statistical models to be developed using cohorts with high disease incidence. This may systematically give overestimated risk estimates when applied to a new unenriched cohort. Recalibration methods (e.g., calibration-in-the-large) may be applied to correct for poor calibration when

performing external validation.[22] Second, this analysis focused on identifying predictors of DI-AKI adjudication in patients with hospital-acquired AKI, making the study findings not applicable to community-acquired DI-AKI or other subtypes of DI-AKI. Third, it is important to acknowledge the potential effect of confounding on our results. We hypothesize that the increased risk of DI-AKI associated with confirmed infection may be confounded by the nephrotoxic antimicrobials prescribed to treat infections in hospitalized patients.[5,35]. For example, a hospitalized patient with bacteremia may receive high doses of vancomycin and piperacillin/tazobactam until stable or culture results favors narrow-spectrum antibiotics. Fourth, it is well-established that drugs have varying degrees of nephrotoxicity. For instance, aminoglycosides are associated with a higher risk of kidney injury compared to cephalosporins.[36,37] Our analysis did not adjust for the varying risk of nephrotoxicity, however, adjudicators inherently associate varying risks according to their knowledge of the literature. The inclusion of drugs' relative nephrotoxicity risk as a variable could potentially improve the model performance in identifying DI-AKI cases.[38] Fifth, in this study, AKI was defined and staged according to the KDIGO criteria. However, the onset of nephrotoxicity for certain drugs (e.g., cisplatin, ifosfamide, proton pump inhibitors) may not fit the KDIGO acute timeline. Additionally, the clinical presentation of nephrotoxicity varies among individual drugs and drug classes depending on the mechanism of injury. For example, aminoglycosides cause ATN, while calcineurin inhibitors may cause different types of injury including hemodynamic insults, ATN or thrombotic microangiopathy. The DIRECT study evaluated a wide spectrum of nephrotoxic drugs that cause injury through various mechanisms. Due to the cohort

size limitation, it was not feasible to analyze drug classes or mechanisms of injury separately. This limitation could affect the generalizability of this research selecting towards mechanisms of nephrotoxicity associated with short-term drug exposure.[39] Since the DIRECT study was completed, new nephrotoxic drugs have been developed and highly utilized (e.g., checkpoint inhibitors) that were not captured in this study.[40] Similarly, new evidence has emerged demonstrating the limitation of SCr as a biomarker for nephrotoxicity due to commonly used drugs. [41,42] This highlights the need for biomarker research to improve the diagnosis of DI-AKI. Lastly, validation with a new cohort was not feasible within the scope of the analysis as the low DI-AKI prevalence would have required the screening and adjudication of a significant number of new AKI cases.[43]

In conclusion, this analysis demonstrates that DI-AKI cases are challenging to distinguish from other AKI subtypes. The IRR of DI-AKI ascertainment is poor, even among experienced nephrologists. Statistical modeling offers a promising comprehensive approach to identifying probable DI-AKI from other AKI subtypes with good performance characteristics. Future studies are needed to externally validate our model and to construct causality assessment tools specific to DI-AKI.

Disclosures & Conflicts of Interest

Supplementary Material

1. Supplemental Table S.1: Candidate nephrotoxic drugs evaluated in DIRECT study. (PDF) Supplementary information is available at KI Report's website.

2. Supplemental Table S.2: Timepoint-pairs referenced to calculate the relative change in Serum Creatinine. (PDF) Supplementary information is available at KI Report's website.

3. Supplemental Table S.3: Distribution of cases by country. (PDF) Supplementary information is available at KI Report's website.

4. Supplemental Table S.4: Rationale for Not DI-AKI adjudication by tiebreaker adjudicator. (PDF) Supplementary information is available at KI Report's website.

5. Supplemental Table S.5: Incidence of AKI risk factors stratified by requiring a tiebreaker adjudicator. (PDF) Supplementary information is available at KI Report's website.

6. Supplemental Table S.6: Kidney biopsy findings. (PDF) Supplementary information is available at KI Report's website.

7. Supplemental Table S.7: List of candidate predictor variables with their domains, timepoints and summary statistics. (PDF) Supplementary information is available at KI Report's website.

8. Supplemental Table S.8: DI-AKI predictors from multivariable logistic regression analysis. (PDF) Supplementary information is available at KI Report's website.

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9. Supplemental Figure S.1: Patient summary as presented in the DIRECT study web platform. (PDF) Supplementary information is available at KI Report's website.

10. Supplemental Figure S.2: Naranjo causality assessment scale. (PDF) Supplementary information is available at KI Report's website.

11. Supplemental Figure S.3: Liverpool causality assessment scale. (PDF) Supplementary information is available at KI Report's website.

12. Supplemental Figure S.4: Clinical adjudication form of DIRECT study. (PDF) Supplementary information is available at KI Report's website.

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Tables

Table 1: Assessment schedule of hospitalized patients in DIRECT study.

	Hospital Admission	Pre-Drug Exposure	Drug Exposure	AKI Onset	Peak SCr or peak severity of injury	Drug Discontinuation	Nadir SCr or Resolution of injury	Hospital Discharge	Status at days 28 and 90
Physical exam	X	X	X	X	X	X	X	X	
AKI risk factors	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	
Laboratory tests	X	X	X	X	X	X	X	X	
SCr	X	X	X	X	X	X	X	X	X
Urine study				X					

KRT				X	X	X	X	X	X
Survival status							X	X

AKI = acute kidney injury; KRT = kidney replacement therapy; SCr = serum creatinine.

Peak SCr or peak severity of injury was defined the highest SCr recorded throughout hospitalization.

This table was adapted from Awdishu, Linda, et al. "Rationale and design of the genetic contribution to Drug Induced Renal Injury (DIRECT) study." *Kidney international reports* 1.4 (2016): 288-298.

Table 2: Characteristics of the cohort.

Characteristics	Entire Cohort (n = 314)	DI-AKI (n = 271)	Not DI-AKI (n = 43)	P-Value
Demographics				
Age, years, median (IQR)	55 (31)	55 (31)	61 (32)	0.09
Race, Caucasian, n (%)	174 (54)	142 (52)	33 (74)	0.13
Male, n (%)	160 (51)	139 (51)	21 (49)	0.87
BSA, m^2, median (IQR)	1.91 (0.28)	1.91 (0.30)	1.91 (0.34)	0.54
ICU admission at AKI onset, n (%)	76 (24.2)	58 (21.4)	18 (41.9)	< 0.01
Baseline eGFR, category, n (%)*				0.40
> 90 mL/min	176 (56.1)	156 (57.6)	20 (46.5)	
60-89 mL/min	67 (21.3)	59 (21.8)	8 (18.6)	
45-59 mL/min	40 (12.7)	33 (12.2)	7 (16.3)	
30-44 mL/min	19 (6.1)	15 (5.5)	4 (9.3)	
15- 29 mL/min	12 (3.8)	8 (3.0)	4 (9.3)	
Past Medical History, n (%)				
Congestive Heart Failure	36 (11.5)	30 (11.1)	6 (14)	0.61
CAD	36 (11.5)	30 (11.1)	6 (14)	0.61

CKD	61 (19.4)	52 (19.2)	9 (20.9)	0.84
COPD	32 (10.2)	30 (11.1)	2 (5)	0.28
Diabetes mellitus	96 (30.6)	89 (32.8)	7 (16)	0.03
Hypertension	140 (44.6)	120 (44.3)	20 (47)	0.87
Leukemia or lymphoma	19 (6.1)	18 (6.6)	1 (2)	0.49
Liver cirrhosis	26 (8.3)	21 (7.7)	5 (12)	0.38
Malignancy – chemotherapy	27 (8.6)	22 (8.1)	5 (12)	0.40
Nephrotoxic Drugs Exposure, n (%)				
Number of candidate nephrotoxic drugs, mean (SD)	1.5 (0.67)	1.5 (0.68)	1.4 (0.63)	0.24
Vancomycin	153 (48.7)	143 (53.8)	10 (23.3)	< 0.01
NSAIDs	57 (18.2)	57 (21.0)	0 (0)	< 0.01
Piperacillin/tazobactam	56 (17.8)	49 (18.1)	7 (16.3)	0.99
Cephalosporin antibiotics	34 (10.8)	23 (8.5)	11 (25.6)	< 0.01
Aminoglycoside antibiotics	30 (9.6)	29 (10.7)	1 (2.33)	0.10
Proton pump inhibitors	27 (8.6)	19 (7.01)	8 (18.6)	0.20
Fluoroquinolone antibiotics	20 (6.4)	15 (5.5)	5 (11.6)	0.17
Other antibiotics	15 (4.8)	14 (5.2)	1 (2.33)	0.70

Calcineurin inhibitor drugs	13 (4.1)	10 (3.7)	3 (7.0)	0.40
Loop diuretics	13 (4.1)	6 (2.2)	7 (16.3)	< 0.01
Antiviral drugs	10 (3.2)	9 (3.3)	1 (2.3)	1.00
Penicillin antibiotics	10 (3.2)	9 (3.3)	1 (2.3)	1.00
Antineoplastic drugs	10 (3.2)	9 (3.3)	1 (2.3)	1.00
Sulfonamide antibiotics	8 (2.5)	7 (2.6)	1 (2.3)	1.00
Antifungal drugs	7 (2.2)	7 (2.6)	0 (0)	0.60
β-lactam antibiotics	7 (2.2)	5 (1.9)	2 (4.7)	0.25
Other drugs	5 (1.6)	4 (1.5)	1 (2.3)	0.52
Antiepileptic drugs	2 (0.6)	2 (0.74)	0 (0)	1.00
ARBs	1 (0.3)	0 (0)	1 (2.3)	0.14
Carbapenem antibiotics	1 (0.3)	1 (0.4)	0 (0)	1.00
Gout suppressant drugs	1 (0.3)	1 (0.4)	0 (0)	1.00

ARBs = angiotensin receptor blockers; BSA = body surface area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; DI-AKI = drug-induced acute kidney injury; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; NSAIDs = nonsteroidal anti-inflammatory drugs.

*eGFR was calculated using serum creatinine between 90 days to 12 months prior to hospital admission.[44]

Table 3: Proportion of AKI risk factors.

AKI Risk Factor, n (%)	Entire Cohort (n = 314)	DI-AKI (n = 271)	Not DI-AKI (n = 43)	P-value
Hyperglycemia	144 (45.86)	131 (48.34)	13 (30.23)	0.03
Severe Infection or sepsis	56 (17.83)	50 (18.45)	6 (13.95)	0.67
Extracellular fluid loss	41 (13.06)	38 (14.02)	3 (6.98)	0.33
Red blood cells transfusion	39 (12.42)	30 (11.07)	9 (20.93)	0.08
Intravascular fluid loss	37 (11.78)	34 (12.55)	3 (6.98)	0.44
Other procedures	31 (9.9)	29 (10.7)	2 (4.7)	0.28
Liver disease	30 (9.55)	24 (8.86)	6 (13.95)	0.27
Anesthetic agent	28 (8.92)	22 (8.12)	6 (13.95)	0.24
Cardiac failure	27 (8.6)	25 (9.23)	2 (4.65)	0.56
Increased vascular capacity	14 (4.46)	9 (3.32)	5 (11.63)	0.03
Cardiac surgery	7 (2.23)	3 (1.11)	4 (9.3)	< 0.01
Vascular surgery	4 (1.27)	3 (1.11)	1 (2.33)	0.45
Hepatorenal syndrome	3 (0.96)	3 (1.11)	0 (0)	1
Hemorrhage	2 (0.64)	2 (0.74)	0 (0)	1

AKI = acute kidney injury; DI-AKI = drug-induced acute kidney injury; RBC = red blood cell

AKI risk factors were considered to be present if they were recorded in the 72 hours preceding AKI onset.

Increased vascular capacity was defined as clinical events leading to reduced blood perfusion (e.g., mean arterial

pressure < 65 mm Hg, sepsis). Hyperglycemia was defined as blood sugar >110 mg/dL or the patient is on insulin.

Table 4: AKI related characteristics and outcomes.

Variable	DI-AKI (n = 271)	Not DI-AKI (n = 43)	P-Value
Previous DI-AKI, n (%)	10 (3.7)	2 (4.8)	1
Start of drug exposure to AKI onset, days, median (IQR)	5 (8)	3 (3.5)	0.24
Baseline SCr, mg/dL, mean (SD)	0.91 (0.44)	0.98 (0.81)	0.60
Peak SCr, mg/dL, mean (SD)	4.5 (2.7)	3.7 (3.2)	0.12
Discharge SCr, mg/dL, mean (SD)	2.2 (1.5)	2.1 (1.4)	0.72
28-days SCr, mg/dL, mean (SD)	1.6 (1.6)	1.6 (1.0)	0.96
90-days SCr, mg/dL, mean (SD)	1.4 (2.0)	1.5 (0.9)	0.28
AKI Stage 3 during hospitalization, n (%)*	194 (73.7)	21 (48.8)	< 0.01
AKD at hospital discharge, n (%)**	166 (61.3)	14 (32.6)	< 0.01
AKD at 28 days, n (%)**	74 (27.3)	11 (25.6)	1
AKD at 90 days, n (%)**	40 (14.8)	5 (11.6)	0.79
Biopsy, n (%)	33 (12.2)	0 (0)	< 0.01
Need for KRT during hospitalization, n (%)	70 (2.6)	11 (2.6)	1
Duration of hospital stay, days, median (IQR)	17 (23)	17 (21)	0.83
Inpatient mortality, n (%)	15 (5.5)	4 (9.3)	0.52

*AKI Stage 3 was defined as 3 times baseline serum creatinine meeting the 2012

Kidney Disease Improving Global Outcomes (KDIGO) criteria.

**AKD was defined as 1.5 x baseline SCr.

AKD = acute kidney disease; AKI = acute kidney injury; DI-AKI = drug-induced acute

kidney injury; IQR = interquartile range; SD = standard deviation; SCr = serum

creatinine; KRT = kidney replacement therapy.

Table 5: Significant DI-AKI predictors from multivariable logistic regression analysis.

Variable	Odds ratio (95% CI)	P-Value
Demographics		
Age, 10 years	0.69 (0.51 – 0.92)	0.01
AKI Risk Factors		
Increased vascular capacity	0.07 (0.01 – 0.54)	0.01
Red blood cells transfusion	0.18 (0.05 – 0.65)	< 0.01
Hyperglycemia	3.72 (1.26 – 12.1)	0.02
Contrast Exposure		
Days between AKI onset and contrast exposure, days	1.08 (1.02 – 1.15)	0.02
Physical Exam		
Confirmed infection	3.84 (1.35 – 11.3)	0.01
Ascites	0.17 (0.04 – 0.74)	0.02
Trends – Labs		
Relative SCr Diff. (Drug Exposure, Pre-Drug Exposure), 10%	0.57 (0.41 – 0.77)	< 0.01
Platelets Diff. (AKI Onset, Drug Exposure), 100×10^9/L	0.40 (0.21 – 0.73)	< 0.01

WBC Diff. (AKI Onset, Drug Exposure), 5 x 10^9/L	0.64 (0.41 - 0.98)	0.04
Urinalysis		
WBC – Heavy, AKI Onset	0.16 (0.03 – 0.84)	0.03

AKI = acute kidney injury; CI =confidence internal; ICU = intensive care unit; SCr = serum creatinine; WBC = white blood cells.

Increased vascular capacity was defined as clinical events leading to reduced blood perfusion to the kidney (e.g., mean arterial pressure < 65 mm Hg, sepsis). Hyperglycemia was defined as blood sugar >110mg/dL or 6.05 mmol/L, or patient is on insulin. Pre-Drug Exposure time point was defined as the day prior to treatment with a candidate nephrotoxic drug. Drug Exposure time point was defined as the first day of treatment with the candidate nephrotoxic drug. AKI Onset time point was defined as the first day of AKI meeting the 2012 Kidney Disease Improving Global Outcomes (KDIGO) AKI stage 2 criteria. Relative SCr Diff. (Drug Exposure, Pre-Drug Exposure) was defined as the relative change in SCr between Drug Exposure and Pre-Drug Exposure time points. WBC in urinalysis was defined as minimal (< 6), moderate (6-20), and heavy (> 21).

Figure Legends

Figure 1:
Flow diagram of subject disposition through DIRECT study and cohort selection.
Legends: AKI = acute kidney injury; CKD = chronic kidney disease; DI-AKI = drug-induced acute kidney injury; DIRECT = Rationale and Design of the Genetic Contribution to Drug Induced Renal Injury Study.
*Cases may meet one or many of the exclusion criteria.

Figure 2:
Mean serum creatinine trends across study time points grouped by DI-AKI ascertainment.
Legends: AKI = acute kidney injury; DI-AKI = drug-induced acute kidney injury.

Figure 3:
Smoothed calibration curves for the observed-to-expected predicted probability plot for the logistic regression model.

Suspected DI-AKI cases assessed for eligibility (n = 1,212)

At least one causal agent
Age ≥ 2 years
(n = 1,151)

Excluded by to DIRECT study eligibility criteria (n = 520)*

- Consent was not obtained (n = 138)
- Patient with a history of kidney transplant (n = 5)
- Patient with a history of bone marrow transplant (n = 2)
- Patient with CKD Stage 5 (n = 4)
- More than 3 causal agents (n = 127)
- No history on time course for drug exposure (n = 18)
- Incomplete data elements (n = 257)

Adjudicated cases
(n = 631)

Excluded by this analysis eligibility criteria (n = 317)*

- Age < 18 years old (n = 140)
- Non-hospitalized patients (n = 172)
- Glomerular injury (n = 7)
- AKI prior to hospital admission (n = 56)

Analyzed cases
(n = 314)

DI-AKI (n = 271)

Not DI-AKI (n = 43)

Logistic Regression Calibration Plot