STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	7	Our research aims to describe the clinical characteristics and predictive variables of DI-AKI.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	7,8	We analysed data from the DIRECT study (NCT02159209), an international, multi-center, observational cohort study of enriched clinically adjudicated DI-AKI cases. Variables associated with DI-AKI were identified using L1 regularized multivariable logistic regression.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	9	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
Objectives	3	State specific objectives, including any prespecified hypotheses	9,10	The aims of this study were to use a well-characterized cohort of clinically adjudicated DI-AKI cases of hospitalized adult

				patients 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.
Methods				
Study design	4	Present key elements of study design early in the paper	11	In this study, we retrospectively analyzed data from hospitalized adult patients, aged 18 years or order, enrolled in the Rationale and Design of the Genetic Contribution to Drug-Induced Renal Injury (DIRECT) study (NCT02159209).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11-13	In summary, DIRECT is an international, multi-center, observational cohort study of enriched DI-AKI cases that underwent clinical adjudication.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	11	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 glomerular phenotype (Figure 1).
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	12,13,14	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).
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	13,14	All cases enrolled in the DIRECT study underwent clinical adjudication by a panel of 9 nephrologists and one pharmacist.
Bias	9	Describe any efforts to address potential sources of bias	11,12	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).
Study size	10	Explain how the study size was arrived at	11,12	Suspected DI-AKI cases identified by the principal investigator at each participating sites were electronically screened for eligibility, enrolled by the site and underwent clinical adjudication.

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12	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.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	14, 15, 16	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.
		(*b*) Describe any methods used to examine subgroups and interactions	N/A	
		(*c*) Explain how missing data were addressed	16	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.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	17	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).
		(b) Give reasons for non-participation at each stage	17	See Figure 1.
		(c) Consider use of a flow diagram	17	See Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	17, 18	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%), as summarized in Table 2. 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).
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	19	See Table 4.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	18, 19	Of the 314 cases, 271 (86%) were adjudicated as DI-AKI with unanimous agreement in 233

				(74.2%) cases, corresponding to ka score of 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).
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A	
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	19, 20	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.
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A	
Discussion				
Key results	18	Summarise key results with reference to study objectives	21	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.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	24, 25	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. 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.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	24	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.
Generalisability	21	Discuss the generalisability (external validity) of the study results	26	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 modelling offers a promising comprehensive approach to identifying probable DI-AKI from other AKI subtypes with good performance characteristics
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27	This study was funded by the International Serious Adverse Events Consortium. Zaid K Yousif acknowledges grant funding from the National Library of Medicine (award number T15LM011271) and the University of California, San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences. Paola Nicoletti is an employee of Sema4 Mount Sinai venture, Stamford, Connecticut, USA. Vivekanand Jha has received grant funding from GSK, Baxter Healthcare, and Biocon and honoraria from AstraZeneca, Boehringer

	Ingelheim, Baxter, NephroPlus and Zydus Cadilla, under the policy of all honoraria being paid to the organization.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.