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Original Article

ORIGINAL ARTICLE

Epidemiology and outcomes of post-AKI proteinuria

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ABSTRACT

Background. Acute kidney injury (AKI) has been associated with increased risks of new-onset and worsening proteinuria. However, epidemiologic data for post-AKI proteinuria was still lacking. This study aimed to determine the incidence, risk factors and clinical correlations of post-AKI proteinuria among hospitalized patients.

Methods. This study was conducted in a multicenter cohort including patients aged 18–100 years with hospital-acquired AKI (HA-AKI) hospitalized at 19 medical centers throughout China. The primary outcome was the incidence of post-AKI proteinuria. Secondary outcomes included AKI recovery and kidney disease progression. The results of both quantitative and qualitative urinary protein tests were used to define post-AKI proteinuria. Cox proportional hazard model with stepwise regression was used to determine the risk factors for post-AKI proteinuria.

Results. Of 6206 HA-AKI patients without proteinuria at baseline, 2102 (33.9%) had new-onset proteinuria, whereas of 5137 HA-AKI with baseline proteinuria, 894 (17.4%) had worsening proteinuria after AKI. Higher AKI stage and preexisting CKD diagnosis were risk factors for new-onset proteinuria and worsening proteinuria, whereas treatment with renin–angiotensin system inhibitors was associated with an 11% lower risk of incident proteinuria. About 60% and 75% of patients with post-AKI new-onset and worsening proteinuria, respectively, recovered within 3 months. Worsening proteinuria was associated with a lower incidence of AKI recovery and a higher risk of kidney disease progression.

Conclusions. Post-AKI proteinuria is common and usually transient among hospitalized patients. The risk profiles for new-onset and worsening post-AKI proteinuria differed markedly. Worsening proteinuria after AKI was associated with adverse kidney outcomes, which emphasized the need for close monitoring of proteinuria after AKI.

LAY SUMMARY

Acute kidney injury (AKI) has been associated with increased risks of new-onset and worsening proteinuria. Increased understanding of post-AKI proteinuria will enhance the knowledge about the interconnection between AKI and chronic kidney disease (CKD). In this large multicenter cohort study, we evaluated the incidence, risk factors and clinical correlations of post-AKI proteinuria among hospitalized patients. We found that post-AKI proteinuria is common and usually transient among hospitalized patients. The risk profiles for new-onset and worsening post-AKI proteinuria differed markedly. Higher AKI stage and preexisting CKD were risk factors for both new-onset and worsening proteinuria, but by contrast, treatment of AKI patients with renin–angiotensin system inhibitors significantly reduced the risk of new-onset proteinuria. Worsening proteinuria was associated with a lower incidence of AKI recovery and a higher risk of kidney disease progression, which emphasized the need for close monitoring of proteinuria after AKI.

Keywords: adults, epidemiology, post-AKI proteinuria, risk factor

INTRODUCTION

Acute kidney injury (AKI) is a common complication among hospitalized patients and is strongly associated with the risk of development of chronic kidney disease (CKD) [1–4]. Proteinuria is an important indicator of CKD and a strong risk factor for progressive loss of renal function [5–7]. Recent studies have indicated that AKI is independently associated with higher risks of incident and worsening proteinuria [8, 9]. Increased understanding of post-AKI proteinuria will enhance the knowledge about the interconnection between AKI and CKD. However, epidemiologic study of post-AKI proteinuria is still lacking. Previous studies did not report detailed clinical characteristics such as the duration, severity and risk factors of post-AKI proteinuria. More importantly, whether new-onset and worsening proteinuria affect the prognosis of AKI is presently unknown.

The present multicenter observational cohort study analyzed 92 102 adult patients with hospital-acquired AKI (HA-AKI) who were hospitalized at 19 medical centers throughout China. This study was designed to determine the incidence and risk factors of new-onset and worsening proteinuria after HA-AKI and to analyze the effects of post-AKI proteinuria on kidney outcomes.

MATERIALS AND METHODS

The study protocol was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University (approval number: NFEC-2019-213), which waived the requirement for patient informed consent due to the retrospective nature of the study. This study was also approved by the China Office of Human Genetic Resources for Data Preservation Application (approval number: 2021-BC0037) and was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [10].

Study design, population and data source

Using the China Renal Data System which has been described in our previous study [11, 12], we conducted a large multicenter retrospective study cohort of 7 084 339 patients hospitalized at 19 medical centers throughout China from 1 January 2000 to 26 May 2021. This database contains information on these patients, both while in hospital and as outpatients. Data recorded included patients' demographic characteristics, such as age, sex, and smoking and drinking status; clinical characteristics, such as blood pressure, vital signs, diagnosis codes at admission and

discharge, dates of diagnosis and drugs prescribed; surgical information, such as dates of operation and operation procedure codes; and laboratory test results, including the time of testing. Prescription data included names, codes, doses, dose units, frequency, route, and start and stop times of all drugs.

The data from all participating hospitals were pooled and analyzed at the National Clinical Research Center for Kidney Disease in Guangzhou, China. All the laboratories of the participating hospitals had passed the annual External Quality Assessment of the Chinese National Center for Clinical Laboratories.

This study included 92 102 hospitalized patients with HA-AKI aged 18–100 years. Patients who did not undergo sufficient (one or more) urinary protein tests before and after the time of HA-AKI diagnosis ($n = 71\,561$) were excluded, as were patients with end-stage renal disease (ESRD) ($n = 2024$), defined as maintenance dialysis or kidney transplantation. Also excluded were patients with baseline estimated glomerular filtration rate (eGFR) $\leq$20 mL/min/1.73 m^2 ($n = 1597$), those with missing prescription ($n = 1004$) or diagnostic ($n = 19$) data, patients with urinary tract infections ($n = 1785$) and pregnant women ($n = 420$). Data obtained at the time of first hospitalization were analyzed in patients who were hospitalized multiple times.

Determination of HA-AKI

AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) creatine criteria [13]. Urine output criteria were not used because urine volume was not available in this study. Methods for determining HA-AKI have been reported in our previous studies [2, 14, 15] and are described in the Supplementary Methods. This study only included patients who developed HA-AKI within 30 days after admission. The earliest day that change in serum creatinine (SCr) level met the KDIGO criteria was defined as the date of AKI onset, or study index date. The stage of AKI was determined based on the peak SCr concentration after AKI detection or initiation of dialysis, with increases of <100% relative to baseline defined as stage 1, 100% to <200% as stage 2, and $\geq$200% or initiation of renal replacement therapy (RRT) as stage 3.

Outcomes and other definitions

The primary outcome was incidence of post-AKI proteinuria. The results of both quantitative and qualitative urinary protein tests were used to determine post-AKI proteinuria. Only urine protein tests performed within 30 days after HA-AKI and before discharge were analyzed. Moreover, the time intervals of urinary protein tests performed before and after AKI had to be $\geq$1 day.

Patients were defined as having new-onset proteinuria after HA-AKI if (i) the results of all available urinary protein tests from admission to AKI onset were negative; and (ii) at least one urinary protein test result after AKI and before discharge was positive. The positive thresholds for quantitative and qualitative urinary protein tests and the grade of new-onset proteinuria are shown in Supplementary data, Table S1. Because the reference range for urine protein-to-creatinine ratio in all our participating hospitals was 0–200 mg/g, we set 200 mg/g as the positive threshold, which has been similarly defined in previous literature [16–18].

Worsening proteinuria was defined using qualitative urinary protein (UPRO) data. Patients were defined as having worsening proteinuria after HA-AKI if (i) the results of all available UPRO tests were positive and less than 4+; and (ii) UPRO level after AKI was at least one grade higher than at baseline, with the latter defined as the highest grade of UPRO before AKI. The definition of worsening proteinuria is shown in Supplementary data, Table S2.

UPRO and quantitative urinary protein (i.e. urine albumin-to-creatinine ratio and 24-h urinary protein excretion) concentrations measured on the same day were highly correlated in the included patients (Supplementary data, Table S3).

The secondary outcomes included kidney disease progression and AKI recovery. Kidney disease progression was defined as: (i) a $\geq$50% reduction in eGFR in patients with baseline eGFR <60 mL/min/1.73 m^2; (ii) a $\geq$30% reduction in eGFR decreased and eGFR <60 mL/min/1.73 m^2 in patients with baseline eGFR $\geq$60 mL/min/1.73 m^2; or (iii) receiving maintenance dialysis or kidney transplantation between 90 days and 2 years after AKI [19, 20]. Patients were defined as having recovered from HA-AKI if their SCr level had decreased to within the non-AKI range and was at least 0.3 mg/dL below the peak level in the absence of RRT [2]. Recovery of post-AKI proteinuria was defined as a return to baseline level of urinary protein or below within 90 days after AKI.

Covariates

All drugs prescribed during hospitalization were classified according to the Anatomical Therapeutic Chemical classification system. Concomitantly administered drugs were coded as dichotomous variables from admission to HA-AKI.

The presence of comorbidities was defined by dichotomous covariates according to International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes at admission and discharge. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [21]. The adjusted clinical procedures were classified as major cardiac, respiratory system, nervous system, urinary system and other procedures according to their ICD-9-CM codes from admission to HA-AKI.

Statistical analyses

Continuous variables were presented as mean (standard deviation) or median (interquartile range), whereas categorical data were presented as number (percentage). Continuous variables were compared by unpaired, two-tailed *t*-tests or Wilcoxon tests, whereas categorical variables were compared by Pearson χ^2 tests.

The Kaplan–Meier method was used to estimate the cumulative incidence of events after HA-AKI. Risk factors for new-onset and worsening proteinuria after AKI were assessed using a Cox proportional hazard model [22] with stepwise regression to screen the baseline variables (see details in Supplementary Methods). The proportional hazards assumption was tested by plotting Schoenfeld residuals against time, followed by visual inspection for uniformity. The rates of AKI recovery stratified by new-onset and worsening proteinuria after AKI were assessed by interval censoring, with comparisons by log-rank tests. We were unable to obtain the exact timing of kidney disease progression, which was very dependent on the frequency of creatinine tests the patient had, thus the associations of new-onset and worsening proteinuria after AKI with kidney disease progression were analyzed by logistic regression models which has also been used in our previous study [23], after adjustment for age, gender, smoking and drinking status, baseline eGFR, intensive care unit (ICU) admission, Charlson Comorbidity Index (CCI), AKI stage, hospital, division, hypertension and

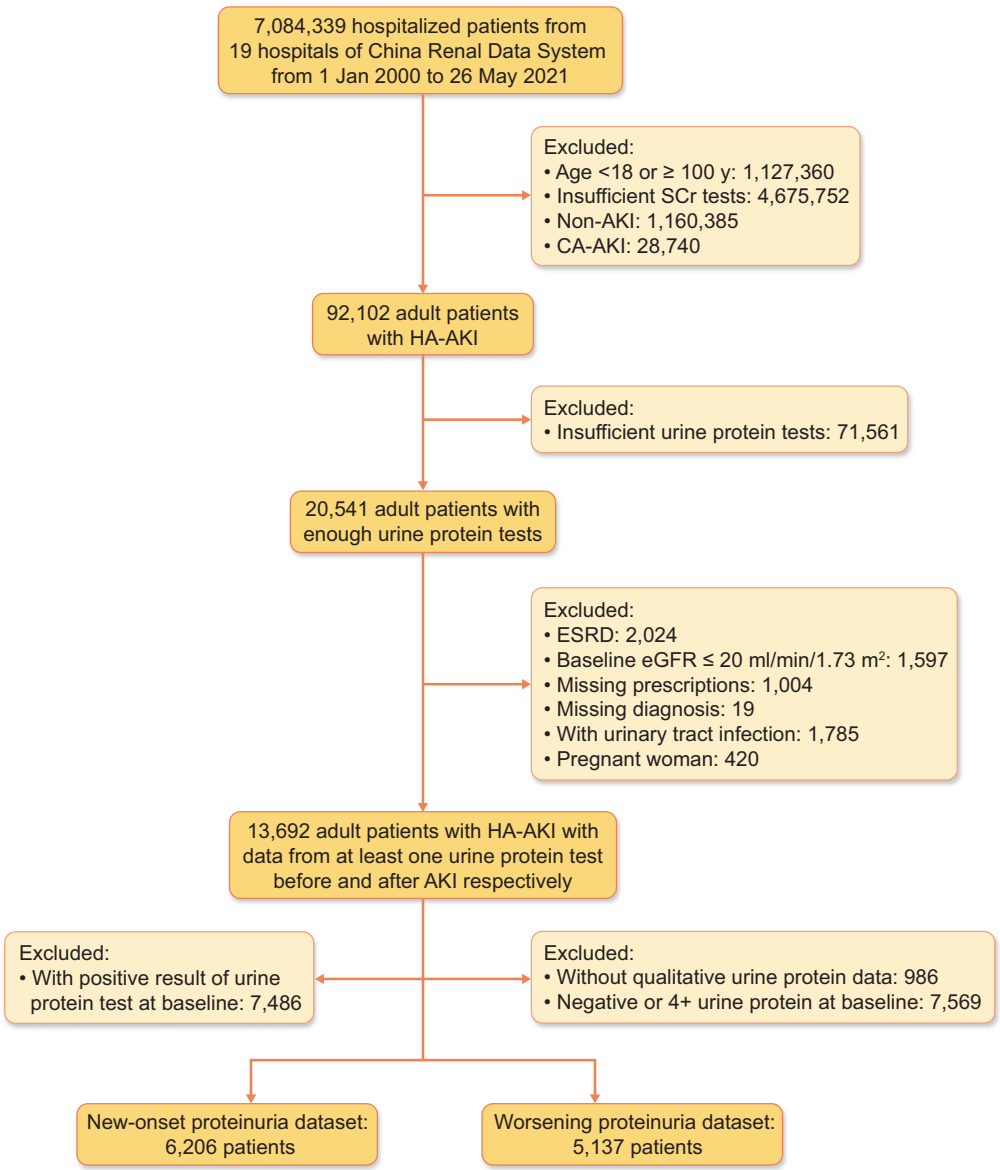

Figure 1: Flowchart of patient selection.

diabetes. In sensitivity analysis, we performed an imputation process using a random forest model for variables with missing rates <30% (see details in Supplementary Methods), to verify the robustness of the above results. Further, we explored the associations between post-AKI proteinuria and kidney disease progression stratified by the recovery status of proteinuria.

All analyses were performed using R, version 3.6.1 (R Foundation for Statistical Computing), with two-tailed *P*-values <.05 considered statistically significant. Data were analyzed from October 2021 to April 2022.

RESULTS

Clinical characteristics and incidence of post-AKI proteinuria

The study population consisted of 13692 patients with HA-AKI who had at least one urinary protein test result each before and after the time of HA-AKI diagnosis. These patients were divided into two separate datasets to analyze new-onset proteinuria and worsening proteinuria after AKI (Fig. 1). The design of this study is shown schematically in Supplementary data, Fig. S1. The characteristics of included and excluded subjects with HA-AKI are summarized in Supplementary data, Table S4.

The clinical characteristics of patients in the two analysis sets stratified by the status of post-AKI proteinuria are summarized in Table 1. Of the 6206 HA-AKI patients who were negative for proteinuria at baseline, 2102 (33.9%) were positive for new-onset proteinuria after AKI. The cumulative incidence of new-onset proteinuria after AKI is shown in Supplementary data, Fig. S2A and B. There was no between-group difference in age, whereas patients with new-onset proteinuria had a lower baseline eGFR, a higher proportion were males, a higher proportion of patients admitted to the ICU and had more severe AKI than patients without new-onset proteinuria ($P < .001$ for all). In 1342

Table 1: Baseline characteristics of the HA-AKI patients stratified by post-AKI proteinuria.

	New-onset proteinuria dataset (*N* = 6206)			Worsening proteinuria dataset (*N* = 5137)		
Variables	Without, N = 4104	With, N = 2102	*P*-value	Without, N = 4243	With N = 894	*P*-value
Age (years)	63.5 (51.1, 73.8)	63.4 (52.4, 72.9)	.79	62.7 (49.2, 74.1)	63.2 (50.5, 74.2)	.16
Male, *n* (%)	2377 (57.9)	1332 (63.4)	<.001	2665 (62.8)	539 (60.3)	.14
Baseline eGFR, mL/min/1.73 m^2	88.8 (66.2, 105.2)	86.5 (65.1, 100.5)	<.001	71.2 (44.8, 95.4)	69.7 (43.6, 94)	.26
Baseline eGFR group, *n* (%)			.91			.21
≤60 mL/min/1.73 m^2	823 (20.1)	424 (20.2)		1688 (39.8)	376 (42.1)	
>60 mL/min/1.73 m^2	3281 (79.9)	1678 (79.8)		2555 (60.2)	518 (57.9)	
ICU	1085 (26.4)	696 (33.1)	<.001	1343 (31.7)	347 (38.8)	<.001
Mechanical ventilation	673 (16.4)	545 (25.9)	<.001	915 (21.6)	246 (27.5)	<.001
Stage AKI, *n* (%)			<.001			<.001
Stage 1	3083 (75.1)	1270 (60.4)		3051 (71.9)	549 (61.4)	
Stage 2	631 (15.4)	418 (19.9)		682 (16.1)	159 (17.8)	
Stage 3	390 (9.5)	414 (19.7)		510 (12)	186 (20.8)	
CCI	4 (3, 6)	5 (3, 6)	.004	4 (3, 6)	5 (3, 6)	.39
LOS, days	22 (15, 33)	24 (16, 39)	<.001	21 (14, 33)	24.5 (15, 39)	<.001
Comorbidities, *n* (%)						
Hypertension	1344 (32.7)	687 (32.7)	.97	1852 (43.6)	381 (42.6)	.59
Diabetes	672 (16.4)	351 (16.7)	.75	987 (23.3)	214 (23.9)	.70
HF	678 (16.5)	424 (20.2)	.001	796 (18.8)	197 (22)	.024
Respiratory failure	294 (7.2)	296 (14.1)	<.001	585 (13.8)	164 (18.3)	<.001
CHD	762 (18.6)	323 (15.4)	.002	624 (14.7)	128 (14.3)	.79
CTD	102 (2.5)	69 (3.3)	.07	328 (7.7)	71 (7.9)	.84
Stroke	688 (16.8)	383 (18.2)	.15	831 (19.6)	171 (19.1)	.78
Sepsis	149 (3.6)	156 (7.4)	<.001	258 (6.1)	75 (8.4)	.01
Malignant tumor	989 (24.1)	655 (31.2)	<.001	745 (17.6)	193 (21.6)	.005
Shock	248 (6)	263 (12.5)	<.001	378 (8.9)	125 (14)	<.001
Liver disease	623 (15.2)	263 (12.5)	.006	507 (11.9)	100 (11.2)	.53
CKD	217 (5.3)	135 (6.4)	.075	1222 (28.8)	256 (28.6)	.93
Concomitant drugs, *n* (%)						
ACEI/ARB	942 (23)	400 (19)	<.001	1230 (29)	218 (24.4)	.008
β blockers	1028 (25)	463 (22)	.010	988 (23.3)	199 (22.3)	.49
CCB	1209 (29.5)	650 (30.9)	.25	1750 (41.2)	348 (38.9)	.19
Diuretics	2021 (49.2)	1062 (50.5)	.35	2522 (59.4)	564 (63.1)	.052
Hypoglycemic drugs	1373 (33.5)	733 (34.9)	.28	1549 (36.5)	322 (36)	.79
Vasopressor drugs	773 (18.8)	522 (24.8)	<.001	772 (18.2)	207 (23.2)	.002
Chemotherapy drugs	360 (8.8)	244 (11.6)	<.001	354 (8.3)	75 (8.4)	1.00
Contrast agent	469 (11.4)	260 (12.4)	.28	350 (8.2)	90 (10.1)	.089
PPIs	2798 (68.2)	1546 (73.5)	<.001	2877 (70.3)	629 (73.4)	.066
NSAIDs	1821 (44.4)	996 (47.4)	.026	1786 (42.1)	375 (41.9)	.95
Statins	970 (23.6)	429 (20.4)	.005	1135 (26.7)	210 (23.5)	.044
Glucocorticoids	1168 (28.5)	640 (30.4)	.09	1405 (33.1)	314 (35.1)	.26
Operation (%)	1720 (41.9)	1031 (49.0)	<.001	1055 (24.9)	264 (29.5)	.006
Laboratory testing indicators[a]						
Blood glucose, mmol/L	5.7 (4.9, 7.4)	5.9 (5.0, 7.8)	.001	6.5 (5.2, 8.7)	6.4 (5.2, 8.8)	.11
White blood cells, 10^9/L	7.2 (5.5, 10)	7.5 (5.7, 10.6)	.044	8.4 (6.1, 12.0)	8.5 (6.0, 12.9)	.66
Total cholesterol, mmol/L	4.2 (3.4, 5.1)	4.2 (3.4, 5.0)	.54	4.3 (3.3, 5.5)	4.3 (3.2, 5.4)	.049
Hemoglobin, g/L	122 (104, 137)	123 (103, 139)	.17	117 (96, 134)	112 (94, 133)	.003
Serum albumin, g/L	37.5 (33.2, 41.3)	37.3 (32.9, 40.7)	.29	33.5 (27.7, 38.6)	33.1 (27.2, 38.3)	.37

Normally distributed continuous variables are represented by mean (standard deviation), skewed continuous variables are represented by median (25% quantile, 75% quantile) and categorical variables are represented by frequency (percentage).

[a]Methods of handling of missing values in Supplementary Methods in the Supplementary data.

LOS, length of stay; CHD, coronary heart disease; HF, heart failure; CTD, connective tissue disease; PPIs, proton pump inhibitors; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

(21.6%) patients prescribed renin–angiotensin system inhibitors (RASi), 351 (26.2%) patients discontinued RASi treatment after HA-AKI, of whom 121 (34.7%) developed new-onset proteinuria (Supplementary data, Table S5).

Of the 5137 HA-AKI adults who were positive for proteinuria at baseline, ranging from trace positive to 3+, 894 (17.4%) were positive for worsening proteinuria after AKI. The cumulative incidence of worsening proteinuria after AKI was shown in Supplementary data, Fig. S2C and D. There were no significant between-group differences in age, gender and baseline eGFR level, but the proportions with severe AKI, ICU admission and need for mechanical ventilation were higher in patients with

Table 2: Clinical factors associated with post-AKI new-onset proteinuria in univariate and multivariate Cox model (stepwise regression).

			Univariate		Multivariate	
Variables	Total *N*	No. of events (%)	HR (95% CI)	*P*-value	aHR (95% CI)	*P*-value
Risk factors						
Stage HA-AKI						
Stage 2	1049	418 (39.8)	1.24 (1.11, 1.39)	<.001	1.26 (1.12, 1.41)	<.001
Stage 3	804	414 (51.5)	1.80 (1.61, 2.01)	<.001	1.70 (1.52, 1.91)	<.001
Mechanical ventilation	1218	545 (44.7)	1.31 (1.18, 1.44)	<.001	1.34 (1.20, 1.51)	<.001
Respiratory failure	590	296 (50.2)	1.60 (1.41, 1.80)	<.001	1.32 (1.15, 1.52)	<.001
Malignant tumor	1644	655 (39.8)	1.22 (1.11, 1.33)	.01	1.14 (1.03, 1.26)	.01
Shock	511	263 (51.5)	1.75 (1.54, 1.99)	<.001	1.29 (1.11, 1.51)	.001
CKD	352	135 (38.4)	1.30 (1.09, 1.55)	.003	1.39 (1.16, 1.66)	<.001
CTD	171	69 (40.4)	1.33 (1.05, 1.69)	.02	1.41 (1.11, 1.81)	.006
Sepsis	305	156 (51.1)	1.45 (1.24, 1.71)	<.001	1.15 (0.96, 1.37)	.12
Chemotherapy drugs	604	244 (40.4)	1.32 (1.16, 1.51)	<.001	1.31 (1.13,1.51)	<.001
NSAIDs	2817	996 (35.4)	1.12 (1.03, 1.22)	.01	1.07 (0.98, 1.17)	.12
Operation	2751	1031 (59.9)	1.25 (1.15, 1.36)	<.001	1.21 (1.10, 1.33)	<.001
Protective factors						
RASi	1342	400 (29.8)	0.87 (0.78, 0.97)	.01	0.89 (0.79, 0.99)	.04
Glucocorticoids	1808	640 (35.4)	0.98 (0.89, 1.08)	.66	0.86 (0.78, 0.96)	.005
Diuretics	3083	1062 (34.4)	0.93 (0.85, 1.01)	.08	0.89 (0.81, 0.97)	.01

CTD, connective tissue disease; HR, hazard ratio; aHR, adjusted hazard ratio.

Table 3: Clinical factors associated with post-AKI worsening proteinuria in univariate and multivariate Cox model (stepwise regression).

			Univariate		Multivariate	
Variables	Total (*N*)	No. of events (%)	HR (95%CI)	*P*-value	aHR (95% CI)	*P*-value
Risk factors						
Female	1933	355 (18.4)	1.09 (0.95, 1.25)	.20	1.13 (0.97, 1.31)	.11
eGFR ≤60 mL/min/1.73 m^2	2064	376 (18.2)	1.14 (1.00, 1.30)	0.06	1.19 (1.02, 1.40)	.03
Stage AKI						
Stage 2	841	159 (18.9)	1.13 (0.95, 1.35)	.17	1.17 (0.96, 1.42)	.12
Stage 3	696	186 (26.7)	1.61 (1.36, 1.90)	<.001	1.54 (1.27, 1.87)	<.001
HF	993	197 (19.8)	1.21 (1.03, 1.42)	.02	1.20 (0.98, 1.47)	.08
Diabetes	1201	214 (17.8)	1.00 (0.86, 1.16)	.97	1.26 (1.02, 1.54)	.04
CKD	1478	256 (17.3)	1.04 (0.90, 1.20)	.60	1.26 (1.02, 1.57)	.03
Operation	1319	264 (20.0)	1.19 (1.03, 1.37)	.02	1.16 (0.97, 1.39)	.06
Protective factors						
ARB	1021	144 (14.1)	0.83 (0.69, 0.99)	.04	0.86 (0.71, 1.06)	.12
Hypoglycemic drugs	1871	322 (17.2)	0.91 (0.79, 1.04)	.16	0.86 (0.72, 1.04)	.10

HF, heart failure; ARB, angiotensin receptor blocker; HR, hazard ratio; aHR, adjusted hazard ratio.

worsening proteinuria after AKI ($P < .001$ for all). In 1448 (28.2%) patients prescribed RASi, 281 (19.4%) patients discontinued RASi treatment after HA-AKI, of whom 53 (18.9%) developed worsening proteinuria (Supplementary data, Table S5).

Of the 1067 patients who had new-onset proteinuria and at least one repeat urine protein test within 90 days after AKI, 655 (61.4%) returned to being negative for proteinuria (Supplementary data, Fig. S3A). Meanwhile, of the 513 patients who had worsening proteinuria and at least one repeat urinary protein test within 90 days after AKI, 383 (74.7%) were observed to recover (Supplementary data, Fig. S3B).

Risk factors for post-AKI proteinuria

The incidence of post-AKI proteinuria in patients with different clinical conditions is presented in Supplementary data, Figs S4 and S5. The two clinical conditions with the highest incidence of new-onset and worsening proteinuria after AKI were shock and sepsis. Multivariate Cox stepwise regression analysis showed that independent risk factors associated with new-onset proteinuria after AKI included the need for mechanical ventilation, severe AKI, respiratory failure, malignant tumor, shock, preexisting CKD, connective tissue disease, use of chemotherapy drugs and surgery, whereas treatment with RASi, glucocorticoids and diuretics were protective factors (Table 2). Similarly, multivariate Cox stepwise regression analysis showed that independent risk factors associated with worsening proteinuria after AKI included severe AKI, preexisting diabetes and preexisting CKD (Table 3). The severity of AKI remained a risk factor for post-AKI proteinuria when restricted to patients in ICU (Supplementary data, Table S6). In sensitivity analysis, after imputing the missing variables, the results remained consistent with the primary analysis (Supplementary data, Tables S7 and S8).

Table 4: The association of post-AKI new-onset and worsening proteinuria with the risk of kidney disease progression.

			Crude model		Adjusted model[a]	
Groups	Total N	Events, N (%)	OR (95% CI)	P-value	aOR (95% CI)	P-value
Post-AKI new-onset proteinuria						
No	1137	256 (22.5)	Ref.		Ref.	
Yes	521	109 (20.9)	0.91 (0.71, 1.17)	.47	0.93 (0.70, 1.23)	.60
Post-AKI worsening proteinuria						
No	1081	342 (31.6)	Ref.		Ref.	
Yes	212	85 (40.1)	1.45 (1.07, 1.96)	.02	1.64 (1.15, 2.32)	<.01

[a]Adjusted for age, sex, status of drinking and smoking, baseline eGFR, ICU admission, CCI, stage AKI, hospital, division, hypertension and diabetes.
Ref., reference.

Association between post-AKI proteinuria and kidney outcomes

Of the 6206 HA-AKI patients without proteinuria at baseline, 5454 (87.9%) had at least one SCr test within 90 days after AKI, of whom 3376 (61.9%) recovered from AKI, including 1235 (64.2%) of the 1925 patients positive for new-onset proteinuria after AKI and 2141 (60.7%) of the 3529 negative for new-onset proteinuria. New-onset proteinuria was not significantly associated with the risks of AKI recovery (Supplementary data, Fig. S6A, $P = .30$) and kidney disease progression [adjusted odds ratio (aOR) 0.93; 95% confidence interval (CI) 0.70–1.23] (Table 4).

Similarly, of the 5137 HA-AKI patients with proteinuria at baseline, 4638 (90.3%) had at least one SCr test within 90 days after AKI, of whom 2685 (57.9%) recovered from AKI, including 476 (56.8%) of the 838 patients positive and 2209 (58.1%) of the 3800 patients negative for worsening proteinuria after AKI. Patients with worsening proteinuria after AKI had a lower incidence of AKI recovery within 90 days (Supplementary data, Fig. S6B, $P < .001$) and an increased risk of subsequent kidney disease progression (aOR 1.64; 95% CI 1.15–2.32) than those without worsening proteinuria (Table 4).

When stratified by the recovery status of proteinuria, the results showed that the ORs in patients with recovery of post-AKI proteinuria seem to be relatively lower than that in patients without recovery (Supplementary data, Table S9).

DISCUSSION

In this large, multicenter cohort of 13 692 HA-AKI patients, 33.9% experienced new-onset and 17.4% experienced worsening proteinuria after AKI. Higher AKI stage and preexisting CKD were risk factors for both new-onset and worsening proteinuria. By contrast, treatment of AKI patients with RASi significantly reduced the risk of new-onset proteinuria. Although most patients with new-onset and worsening proteinuria recover from these conditions within 3 months, worsening proteinuria was associated with a lower rate of AKI recovery and a higher risk of kidney disease progression.

AKI has been recognized as a worldwide public health problem, affecting nearly 20% of hospitalized patients and increasing in incidence by 10% every year [24, 25]. Optimal care for AKI patients remains undetermined, and additional information about risk factors for proteinuria after AKI may help in formulating therapeutic strategies that optimize post-AKI care. The finding of this study, namely that potentially nephrotoxic drugs, such as chemotherapy agents, non-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics, may play a role in the development of post-AKI proteinuria, indicates the need to monitor use of these drugs in patients who experience AKI. By contrast, treatment with RASi was associated with an 11% lower risk of new-onset proteinuria and a 14% lower risk of worsening proteinuria after AKI. Although several previous studies showed that RASi reduced the level of proteinuria in patients with CKD [26, 27], it was unclear whether these agents could also modify post-AKI proteinuria. The present results showed that treatment with RASi might contribute to the prevention and treatment of post-AKI proteinuria, which might further affect the prognosis of patients with AKI.

HA-AKI is associated with a higher risk of in-hospital mortality and AKI survivors are at significantly increased risk of developing CKD [28, 29]. Proteinuria following AKI may explain, at least in part, the potential mechanisms linking AKI and CKD progression. AKI has been associated with new-onset proteinuria, emphasizing the need to assess the clinical significance of proteinuria after AKI [8, 9]. A higher urine albumin-to-creatinine ratio 3 months after discharge in patients hospitalized for AKI was found to be associated with an increased risk of kidney disease progression [30]. That study, however, did not measure baseline proteinuria level, nor was it known whether proteinuria was present before the AKI episode or only after AKI. The present study examined the prognostic implications of both new-onset and worsening proteinuria, including their adverse effects on AKI recovery and subsequent kidney disease progression. Because changes in proteinuria level after AKI are assessed in relatively few patients, these findings emphasize the importance of close follow-up and monitoring of urinary protein after AKI.

The physiological mechanism underlying post-AKI proteinuria remains unclear. Risk factors for new-onset proteinuria and worsening proteinuria after AKI differed markedly, as did patient prognosis, suggesting that different mechanisms may be responsible for new-onset and worsening proteinuria after AKI. Animal models of renal ischemia–reperfusion injury showed that the risk of proteinuria after AKI was increased [31]. The present study found that shock, respiratory failure and mechanical ventilation were risk factors for incident proteinuria after AKI, suggesting that hypoxic-ischemic damage may play a potential pathogenic role in the development of post-AKI proteinuria. Alternatively, post-AKI proteinuria may be caused by AKI-related renal tubular damage, including impaired proximal tubular uptake of filtered albumin and other low molecular weight proteins [32, 33]. This hypothesis was supported by findings showing that chemotherapy agents, antibiotics and NSAIDs, all of which are considered causes of acute tubulointerstitial injury, were associated with an increased risk of post-AKI proteinuria. These findings provide pathophysiologic insight

and may generate mechanistic hypotheses useful for future research.

The major strength of the present study was the use of a large, multicenter patient cohort with extensive patient-level data. This allowed the detailed analyses of risk profiles and adjustments for possible confounders. The present study also had several limitations, including its retrospective design, which likely resulted in selection biases. For example, the study cohort only included patients with a sufficient number of serum creatinine and proteinuria measurements. Patients requiring more frequent monitoring may have more severe disease. However, the large sample size, including wide ranges of disease spectra and severities, ensured rigorous adjustment for possible confounders. In addition, baseline and post-AKI proteinuria were assessed using both quantitative and semi-quantitative parameters, preventing comparisons of results obtained using different methods. However, the results of quantitative and qualitative measurements of urinary protein in individuals on the same day were highly correlated. Another limitation was that proteinuria after discharge was monitored in relatively few patients, which made it more difficult methodologically to evaluate longitudinal changes in post-AKI proteinuria.

In conclusion, the present study examined the incidences and different risk profiles for new-onset and worsening proteinuria after AKI. Administration of RASi before AKI might reduce the risk of new-onset proteinuria, suggesting that risk of post-AKI proteinuria was potentially modifiable. Although most post-AKI proteinuria is transient, its high incidence and significant prognostic implications emphasize the need for close monitoring of proteinuria after AKI.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

AUTHORS' CONTRIBUTIONS

X.X. and S.N. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. L.S., Y.L., R.C. and X.Z. contributed equally as co-first authors. X.X. and S.N. contributed to the study design. S.N. and L.S. drafted the manuscript. S.N., L.S. and X.X. contributed to the statistical analysis. Y.C., F.L., R.X., Q.G., R.C., M.P., S.Z., Y.H., H.Li, Q.Y., Q.W., B.L., H.X., G.L., J.W., G.X., C.C., H.Liu, Y.S., Y.Zha, Y.K., G.S., Y.T., Y.Zhou and M.G. contributed to the data acquisition.

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DATA AVAILABILITY STATEMENT

De-identified individual level-data are available upon request to S.N. at niesheng0202@126.com

CONFLICT OF INTEREST STATEMENT

All the authors declared no competing interests.

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