

Association of Urine Albumin-Creatinine Ratio and Cystatin C-Based Estimated GFR with Outcomes in Patients with Ischemic Stroke

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Keywords

Urine albumin-creatinine ratio · Cystatin C-based estimated GFR · Ischemic stroke

Abstract

Background/Aims: Data about the independent and combined effects of cystatin C-based estimated glomerular filtration rate (eGFR_{cys}) and albuminuria on the risk of poor outcome in stroke patients are limited. The aim was to elucidate how these two renal markers affect the clinical outcomes after ischemic stroke separately and jointly. **Methods:** The study subjects consisted of 10,197 patients with ischemic stroke from the third China National Stroke Registry. The study outcomes were all-cause mortality, poststroke disability, recurrence of stroke, and cardiocerebral vascular disease (CVD) composite events. Cox proportional hazard models and multivariable logistic regression model were applied to evaluate the effects of eGFR_{cys} and urine albumin-creatinine ratio (ACR) on these outcomes. **Results:** Both reduced eGFR_{cys} and increased ACR were independently associated with higher incidences of all-cause death and poststroke disability ($p < 0.01$). Mildly decreased eGFR_{cys} (60–89 mL/min/1.73 m²) is associated with increased risk of all-cause

death and poststroke disability in the presence of high-normal ACR (10–29 mg/g). Patients with both eGFR_{cys} <45 mL/min/1.73 m² and ACR ≥30 mg/g at baseline had a 6.8-fold risk for all-cause mortality and 3.6-fold risk for poststroke disability, compared with patients with eGFR_{cys} of 90–119 mL/min/1.73 m² and ACR <10 mg/g. In addition, increased ACR was associated with recurrent stroke and CVD composite event, while reduced eGFR_{cys} showed no relationship with these outcomes. **Conclusions:** Both decreased eGFR_{cys} and albuminuria are independent risk factors for all-cause death and poststroke disability. Combining the two markers is useful for improving risk stratification even in those without chronic kidney disease.

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Introduction

Emerging data suggest positive association between kidney damage manifested by increased albuminuria or decreased estimated glomerular filtration rate (eGFR) with cerebrovascular and cardiovascular disease in the

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stroke patients [1–8] as well as general population [9–13]. As an alternative filtration marker, cystatin C-based eGFR (eGFR_{cys}) has a stronger association with mortality and cardiovascular disease than does eGFR based on creatinine (eGFR_{cr}) and improves risk stratification [14–16]. However, studies investigating the prognostic roles of albuminuria for adverse clinical outcomes among post-stroke patients are mostly small-sample sized and short-term followed, and the predictive value of eGFR_{cys} for stroke outcome remains unclear [17, 18]. Furthermore, no studies have evaluated the independent and combined effects of eGFR_{cys} and albuminuria on the risk of poor stroke outcome in a large prospective stroke cohort.

The purpose of the present study is to describe the effect of decreased eGFR_{cys} and increased urine albumin-creatinine ratio (ACR) alone and in combination of both on the all-cause mortality, poststroke disability, recurrence of stroke, and cardiocerebral vascular disease (CVD) composite events in patients with ischemic stroke. Meanwhile, since prior studies suggest that even minor anomaly in eGFR and urine ACR predict vascular risks [11, 19], there is a need to explore the combined association of these markers in categories that are lower than the current clinical cutoffs for defining chronic kidney disease (CKD).

Methods

Study Population

Our source population included participants from the third China National Stroke Registry (CNSR-III), a nationwide clinical registry of ischemic stroke or TIA in China. In the CNSR-III cohort, 15,166 patients were enrolled between August 2015 and March 2018. Details of the CNSR-III cohort are described elsewhere [20]. In the present study, we included participants who had serum cystatin C and urinary ACR centrally measured, and with 1-year follow-up data from CNSR-III.

The baseline data of included patients was collected within 24 h after admission through a face-to-face interview by research coordinators. Medical history included a history of diabetes, hypertension, and coronary heart disease, and atrial fibrillation. Baseline information included age, sex, and body mass index. Stroke severity was assessed by the National Institute of Health Stroke Scale (NIHSS) and disability was assessed by the modified Rankin Scale (mRS) within 24 h of admission.

Measurements

Blood and urine samples were collected by the first day of enrollment (within 24 h). All the blood and urine samples were frozen in cryotube at -80°C refrigerator. The samples were transported through cold chain to the centre laboratory in Beijing Tiantan Hospital, where all serum and urine specimens were stored at -80°C until testing was performed. The value of serum cystatin C was measured by the immunoturbidimetric method (Roche cobas

c501 analyzer with cystatin C assay), which has an approximate coefficient of variation of 2%. The values of eGFR_{cys} were calculated using the equations from the Chronic Kidney Disease Epidemiology Collaboration [16]. Participants were categorized into 5 eGFR_{cys} categories: ≥ 120 , 90–119, 60–89, 45–59, and < 45 mL/min/1.73 m². Urine ACR was estimated in mg albumin/g creatinine (mg/g). Participants were categorized into 3 categories based on urine ACR level: optimal (< 10 mg/g), high-normal (10–29 mg/g), and albuminuria (≥ 30 mg/g). Study technicians running the assays were blinded to the participant's clinical information.

Outcome Assessment

Clinical outcomes included all-cause death, stroke recurrence, and CVD composite event which occurred during 1-year, and poststroke disability at 1-year. Death was confirmed either by the death certificates from the attended hospital or the local citizen registry. Poststroke disability was defined by scores on the mRS range from 3 to 6. Stroke recurrence included ischemic stroke and haemorrhagic stroke. CVD composite event included ischemic stroke, haemorrhagic stroke, myocardial infarction, or vascular death.

Statistical Analysis

eGFR of 90–119 mL/min/1.73 m² and ACR < 10 mg/g were used as the reference category. Continuous variables between groups were compared using ANOVA test, or Mann-Whitney U test; categorical variables were compared using χ^2 test. Cox proportional hazard models were used to estimate hazard ratios (HRs) for all-cause mortality, recurrence of stroke, and CVD composite events. Multivariable logistic regression model was used for assessment of variables that were associated with poststroke disability by calculating odds ratio (OR) and 95% CI. Models were adjusted for clinically potential relevant covariates including age, sex, hypertension, diabetes, coronary heart disease, atrial fibrillation, current smoking, total cholesterol level, NIHSS score, and mRS on admission. Interaction between eGFR_{cys} and ACR was assessed using ACR as a categorical variable, using likelihood ratio test to compare models.

Results

General Characteristics of all Participants

Of the 15,166 patients with ischemic stroke or TIA consecutively enrolled in the CNSR-III, 3,905 (25.7%) participants from 30 study sites did not participate the biomarker study; in addition, 768 patients were excluded for lack of ACR and 296 for lack of serum cystatin C data at baseline. Eventually, 10,197 patients were included in the study, including 6,990 men and 3,207 women. There were 274 (2.7%), 3,350 (32.9%), 4,778 (46.9%), 1,222 (12.0%), and 573 (5.6%) patients classified into eGFR_{cys} ≥ 120 , 90–119, 60–89, 45–59, and < 44 mL/min/1.73 m², respectively. Meanwhile, 5,871 (57.6%), 1,892 (18.6%), and 2,434 (23.9%) patients were classified into ACR groups < 10 , 10–29, ≥ 30 mg/g, respectively. Baseline char-

acteristic data in five eGFR_{cys} categories and three ACR categories are listed in Table 1. Compared with patients with higher eGFR_{cys} or lower ACR, those with lower eGFR_{cys} or higher ACRs were likely to be older; have lower proportion of male; a higher prevalence of current smokers, diabetes, hypertension, atrial fibrillation, coronary heart disease; a higher mean total cholesterol, creatinine, cystatin C, NIHSS score, and mRS on admission. While patients with eGFR \geq 120 mL/min/1.73 m² were likely to be younger, male, have higher BMI, and higher prevalence of diabetes compared with those with eGFR 90–119 mL/min/1.73 m². Table 2 shows the proportions of patients in each eGFR_{cys} and urine ACR category. The majority of participants had urine ACR <10 mg/g except those with eGFR_{cys} <45 mL/min/1.73 m². For those with eGFR_{cys} of <120 mL/min/1.73 m², a stepwise increase in the prevalence of ACR \geq 30 mg/g was identified as eGFR decreased.

Outcomes

Crude Incidence Rates

Table 3 shows unadjusted incidence rates for all the four outcomes. A total of 323 (3.17%) deaths, 1,283 (12.58%) poststroke disability events, 1,004 (9.84%) stroke recurrence, and 1,059 (10.39%) CVD events occurred during a median follow-up of 1 year. Incidence rates for all events were higher in those in the lower baseline eGFR_{cys} categories or those with higher ACR. The 1-year cumulative incidence of all-cause death in patients with an eGFR \geq 120, 90–119, 60–89, 45–59, and <45 mL/min/1.73 m² were 2.19, 1.34, 2.99, 6.06, and 9.60%, respectively. Those of poststroke disability were 9.7, 9.0, 12.5, 20.2, and 25.9%, respectively.

When participants were classified by urine ACR at baseline, the 1-year cumulative incidences of all-cause death with ACR <10, 10–29, \geq 30 mg/g were 1.77, 2.59, and 6.98%, respectively, while those of poststroke disability were 8.57, 13.32, and 23.09%, respectively. Substantially higher incidence rates were observed across ACR categories within the same eGFR_{cys} category. For example, in the eGFR_{cys} category of 60–89 mL/min/1.73 m², the incidence rate of all-cause mortality was nearly 3.7 fold as high for those with ACR of \geq 30 mg/g (6.63%) compared with those with ACR <10 mg/g (1.79%) (Table 4).

Independent Associations of eGFR_{cys} and ACR with Outcome

As shown in Table 3 and Figure 1, eGFR_{cys} did not suggest the risk of recurrent stroke and CVD composite event. However, reduced eGFR_{cys} was a significant risk

Table 1. Baseline characteristics stratified by eGFR_{cys} and ACR

	eGFR _{cys} , mL/min/1.73m ²					ACR, mg/g			p value
	\geq 120	90–119	60–89	45–59	<45	<10	10–29	\geq 30	
N	274	3,350	4,778	1,222	573	5,871	1,892	2,434	
Age, years	49.3±11.2	56.6±9.6	63.9±9.9	70.5±9.9	70.4±1.2	61.18±10.91	63.28±11.22	64.15±11.81	<0.001
Male, n (%)	213 (77.7)	2,296 (68.5)	3,289 (68.8)	830 (67.9)	362 (63.2)	4,286 (73.00)	1,199 (63.37)	1,505 (61.83)	<0.001
BMI, kg/m ²	25.5±3.8	24.8±3.2	24.7±3.3	24.4±3.7	24.6±3.6	24.67±3.19	24.73±3.44	24.73±3.56	0.7673
Current smoker, n (%)	95 (34.7)	1,156 (34.5)	1,537 (32.2)	324 (26.51)	123 (21.4)	2,058 (35.05)	533 (28.17)	644 (26.46)	<0.001
Diabetes, n (%)	76 (27.7)	843 (25.2)	1,024 (21.4)	289 (23.7)	181 (31.6)	1,033 (17.59)	500 (26.43)	880 (36.150)	<0.001
Hypertension, n (%)	152 (55.4)	1,972 (58.9)	3,009 (63.0)	852 (69.7)	419 (73.1)	3,353 (57.11)	1,313 (69.40)	1,738 (71.41)	<0.001
Atrial fibrillation, n (%)	3 (1.09)	95 (2.84)	344 (7.2)	166 (13.58)	100 (17.45)	280 (4.77)	162 (8.56)	266 (10.93)	<0.001
Coronary artery disease, n (%)	16 (5.8)	235 (7.0)	544 (11.4)	204 (16.7)	113 (19.7)	557 (9.49)	223 (11.79)	332 (13.64)	<0.001
Total cholesterol, mmol/L	4.4±1.6	4.1±1.2	4.1±1.2	4.1±1.2	4.3±1.5	4.06±1.18	4.12±1.20	4.24±1.28	<0.001
Creatinine, μ mol/L	56.9±16.4	62.9±15.7	72.3±19.3	85.3±23.4	126.0±83.9	71.57±20.71	70.65±22.64	80.13±49.65	<0.001
Cystatin C, mg/g	0.53±0.15	0.8±0.1	1.0±0.1	1.3±1.0	1.8±0.5	0.96±0.22	0.97±0.24	1.10±0.42	<0.001
mRS	2.0±1.5	1.8±1.4	1.8±1.4	2.1±1.4	2.1±1.4	1.75±1.33	1.95±1.41	2.17±1.50	<0.001
NIHSS score	4.0 (2.0–7.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	3.0 (2.0–6.0)	4.0 (2.0–7.0)	3.0 (1.0–5.0)	3.0 (1.0–6.0)	4.0 (2.0–7.0)	<0.001
eGFR _{cys} , mL/min/1.73 m ²	137.7±29.4	102.2±7.9	75.6±8.4	53.6±4.3	35.2±7.9	83.72±21.43	81.90±22.72	74.17±26.09	<0.001
ACR, mg/g	6.93 (2.3–25.9)	5.70 (2.0–21.1)	6.03 (1.9–22.0)	12.65 (3.2–50.4)	49.92 (6.93–394.8)	2.6 (1.1–5.0)	16.7 (12.9–21.8)	89.3 (49.3–246.0)	<0.001

ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C-based estimated glomerular filtration; NIHSS, national institutes of health stroke scale; BMI, body mass index.

Table 2. Prevalence of ACR in each category of eGFR_{cys}

eGFR _{cys} , mL/min/1.73m ²	ACR, mg/g			Overall
	<10	10–29	≥30	
≥120	159 (58.03)	54 (19.71)	61 (22.26)	274 (2.69)
90–119	2,077 (62.00)	636 (18.99)	637 (19.01)	3,350 (32.89)
60–89	2,902 (60.74)	866 (18.12)	1,010 (21.14)	4,778 (46.90)
45–59	566 (46.32)	260 (21.28)	396 (32.41)	1,222 (12.00)
<45	167 (29.14)	76 (13.26)	330 (57.59)	573 (5.62)
Overall	5,871 (57.58)	1,891 (18.55)	2,434 (23.87)	10,197

ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C-based estimated glomerular filtration.

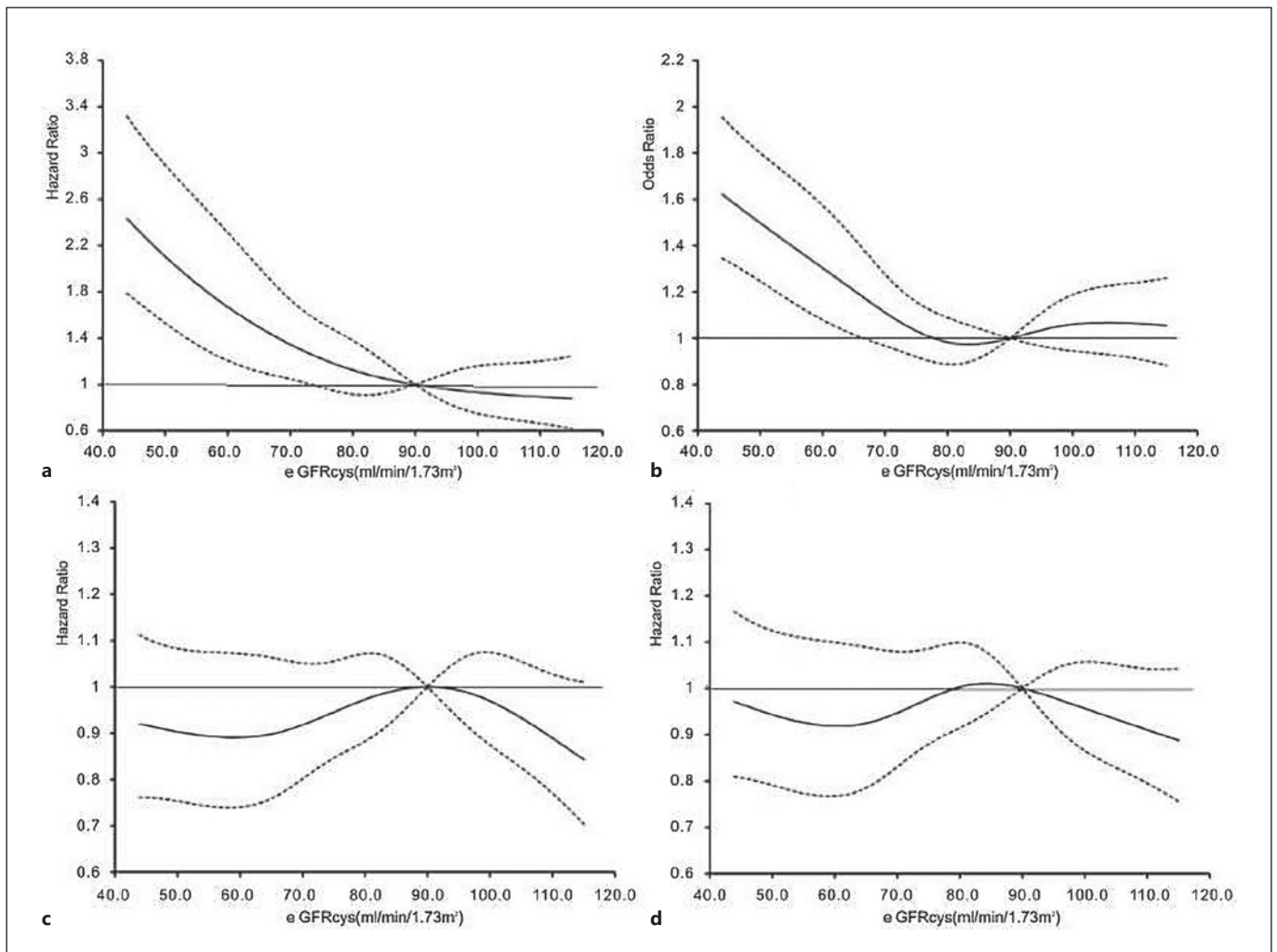


Fig. 1. HRs with 95% confidence intervals of eGFR_{cys} with the all-cause mortality (a), recurrence of stroke (c), CVD composite events (d), and ORs with 95% confidence intervals of eGFR_{cys} with the poststroke disability (b). Reference group is eGFR_{cys} of 90–119 mL/min/1.73 m².

Table 3. Adjusted HRs or ORs of outcomes stratified by eGFR_{cys} or ACR categories alone

eGFR _{cys} , mL/min/1.73m ²	All-cause death		Poststroke disability		Recurrent stroke		CVD composite event	
	event rate, n (%)	HR (95% CI)	event rate, n (%)	OR (95% CI)	event rate, n (%)	HR (95% CI)	event rate, n (%)	HR (95% CI)
≥120	6/274 (2.19)	0.88 (0.56–1.37)	26/268 (9.7)	0.99 (0.65–1.45)	21/274 (7.66)	0.88 (0.56–1.37)	24/274 (8.76)	0.99 (0.65–1.45)
90–119	45/3,350 (1.34)	1.0 (reference)	295/3,280 (9.0)	1.0 (reference)	304/3,350 (9.07)	1.0 (reference)	313/3,350 (9.34)	1.0 (reference)
60–89	143/4,778 (2.99)	1.56 (1.10–2.21)	581/4,650 (12.5)	1.11 (0.94–1.32)	486/4,778 (10.17)	1.03 (0.89–1.20)	513/4,778 (10.74)	1.05 (0.90–1.22)
45–59	74/1,222 (6.06)	2.23 (1.49–3.35)	239/1,186 (20.2)	1.42 (1.14–1.78)	129/1,222 (10.56)	0.97 (0.78–1.22)	137/1,222 (11.21)	0.98 (0.79–1.22)
<45	55/573 (9.60)	3.25 (2.11–5.00)	142/557 (25.9)	1.91 (1.46–2.48)	64/573 (11.17)	1.00 (0.75–1.34)	72/573 (13.41)	1.07 (0.82–1.41)
ACR, mg/g								
<10	104/5,871 (1.77)	1.0 (reference)	492/5,741 (8.57)	1.0 (reference)	486/5,871 (8.28)	1.0 (reference)	509/5,871 (8.67)	1.0 (reference)
10–29	49/1,892 (2.59)	1.16 (0.83–1.64)	245/1,840 (13.32)	1.35 (1.13–1.61)	192/1,892 (10.15)	1.18 (0.99–1.39)	204/1,892 (10.78)	1.19 (1.01–1.40)
≥30	170/2,434 (6.98)	2.39 (1.84–3.09)	546/2,365 (23.09)	2.12 (1.83–2.46)	326/2,434 (13.39)	1.52 (1.32–1.76)	346/2,434 (14.22)	1.54 (1.33–1.77)

All HRs and ORs adjusted for age, sex, hypertension, diabetes, coronary heart disease, atrial fibrillation, current smoking, total cholesterol level, NIHSS score, and mRS on admission. ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C-based estimated glomerular filtration.

factor for all-cause death and poststroke disability. Compared with the reference eGFR_{cys} of 90–119 mL/min, the HRs for all-cause mortality were 1.56 in those with eGFR_{cys} of 60–89 mL/min (95% CI: 1.10–2.21), 2.23 in those with eGFR_{cys} of 45–59 mL/min (95% CI: 1.49–3.35), and 3.25 in those with eGFR_{cys} of <45 mL/min (95% CI: 2.11–5.00). The ORs for stroke disability was 1.42 (95% CI: 1.14–1.78) for those with eGFR_{cys} of 45–59 mL/min/1.73 m², and 1.9 (95% CI: 1.46–2.49) for those with eGFR_{cys} of <45 mL/min/1.73 m².

As shown in Table 3 and Figure 2, compared to patients with ACR <10 mg/g, risks for CVD composite event (HR 1.19; 95%CI, 1.01–1.40) and poststroke disability (OR 1.35; 95%CI: 1.13–1.61) in patients with ACR 10–29 mg/g were significantly higher, while ACR ≥30 mg/g were associated with increase in risk of all these four poor outcomes. The relationship of ACR to the relative risk of the adverse outcomes was monotonic with HRs or ORs increasing linearly with increasing ACR, without threshold effects.

Combined Associations of eGFR and ACR with All-Cause Mortality and Poststroke Disability

HRs and ORs were calculated in fifteen subgroups classified according to eGFR_{cys} and category of urine ACR to determine the joint effect of these renal biomarkers on the risk of all-cause mortality and poststroke disability. As shown in Table 4, in the ACR category of <10 mg/g, HRs were 3.34 (95% CI: 1.73–6.45) and 3.41 (95% CI: 1.45–7.98) in those with eGFR_{cys} of 45–59 and <45 mL/min/1.73 m², respectively, for the all-cause mortality. In the ACR category of ≥30 mg/g, HRs for all-cause mortality were 9.00 (95% CI: 2.96–27.43) for those with eGFR_{cys} of ≥120 mL/min/1.73 m², and for those with eGFR_{cys} of <120 mL/min/1.73 m², a stepwise increase in the HRs was identified as eGFR decreased. When the results were analyzed according to the stage of eGFR_{cys}, the risk for all-cause mortality generally increased as urinary ACR rised. Patients with both eGFR_{cys} <45 mL/min/1.73 m² and ACR ≥30 mg/g at baseline had a 6.8-fold higher risk for all-cause mortality, compared with the reference group. The interaction *p* value for ACR and eGFR_{cys} with all-cause mortality was 0.095.

When compared with the reference group, in the ACR 10–29 mg/g categories, risks for poststroke disability were 1.81 (95% CI: 1.36–2.41) and 2.11 (95% CI: 1.13–3.92) in patients with eGFR_{cys} 60–89 and <45 mL/min/1.73 m², respectively. While the ORs significantly increased in all eGFR_{cys} categories when ACR was ≥30 mg/g. Patients with both eGFR_{cys} <45 mL/min/1.73 m² and ACR ≥30 mg/g at baseline had a more than 3-fold risk for post-

Table 4. Adjusted HRs or ORs of outcomes stratified by combination of eGFR_{cys} and ACR categories

eGFR _{cys} , mL/min/1.73m ²	ACR, mg/g					
	<10		10–29		≥30	
	event rate, <i>n</i> (%)	HR (OR) (95% CI)	event rate, <i>n</i> (%)	HR (OR) (95% CI)	event rate, <i>n</i> (%)	HR (OR) (95% CI)
All-cause death						
≥120	2/159 (1.26)	2.07 (0.47–9.08)	0/54 (0)	0	4/61 (6.56)	9.00 (2.96–27.43)
90–119	15/2,077 (0.72)	1.0 (reference)	6/636 (0.94)	1.07 (0.42–2.76)	24/637 (3.77)	3.85 (2.02–7.37)
60–89	52/2,902 (1.79)	1.77 (0.99–3.17)	24/866 (2.77)	2.31 (1.20–4.46)	67/1,010 (6.63)	4.81 (2.70–8.56)
45–59	26/566 (4.59)	3.34 (1.73–6.5)	12/260 (4.62)	2.76 (1.26–6.05)	36/396 (9.09)	5.14 (2.73–9.7)
<45	9/167 (5.39)	3.41 (1.45–7.98)	7/76 (9.21)	5.51 (2.20–13.84)	39/330 (11.82)	6.81 (3.64–12.75)
Poststroke disability						
≥120	10/155 (6.45)	1.17 (0.56–2.41)	4/53 (7.55)	1.11 (0.36–3.41)	12/60 (20)	2.66 (1.24–5.69)
90–119	127/2,034 (6.24)	1.0 (reference)	54/621 (8.7)	1.16 (0.811.65)	114/625 (18.24)	2.41 (1.79–3.24)
60–89	244/2,836 (8.6)	1.10 (0.86–1.39)	128/838 (15.27)	1.81 (1.36–2.41)	209/981 (21.3)	2.17 (1.67–2.83)
45–59	88/553 (15.91)	1.62 (1.18–2.24)	42/253 (16.6)	1.42 (0.94–2.16)	109/380 (28.68)	2.67 (1.93–3.71)
<45	23/163 (14.11)	1.21 (0.72–2.02)	17/75 (22.67)	2.11 (1.13–3.92)	102/319 (31.97)	3.64 (2.59–5.10)
Recurrent stroke						
≥120	11/159 (6.92)	0.92 (0.50–1.71)	3/54 (5.56)	0.70 (0.22–2.18)	7/61 (11.48)	1.43 (0.67–3.05)
90–119	163/2,077 (7.85)	1.0 (reference)	56/636 (8.81)	1.08 (0.80–1.46)	85/637 (13.34)	1.63 (1.25–2.12)
60–89	252/2,902 (8.68)	1.02 (0.84–1.25)	94/866 (10.85)	1.24 (0.95–1.61)	140/1,010 (13.86)	1.56 (1.23–1.97)
45–59	47/566 (8.3)	0.90 (0.64–1.26)	31/260 (11.92)	1.23 (0.83–1.84)	51/396 (12.88)	1.36 (0.98–1.89)
<45	13/167 (7.78)	0.81 (0.45–1.43)	8/76 (10.53)	1.08 (0.53–2.22)	43/330 (13.03)	1.38 (0.97–1.95)
CVD composite event						
≥120	12/159 (7.55)	1.00 (0.55–1.79)	5/54 (9.26)	1.14 (0.47–2.79)	7/61 (11.48)	1.41 (0.66–3.00)
90–119	167/2,077 (8.04)	1.00 (reference)	56/636 (8.81)	1.05 (0.78–1.43)	90/637 (14.13)	1.68 (1.30–2.18)
60–89	264/2,902 (9.1)	1.04 (0.85–1.27)	101/866 (11.66)	1.29 (1.0–1.66)	148/1,010 (14.65)	1.60 (1.27–2.01)
45–59	50/566 (8.83)	0.92 (0.66–1.27)	32/260 (12.31)	1.22 (0.82–1.80)	55/396 (13.89)	1.40 (1.02–1.93)
<45	16/167 (9.58)	0.95 (0.56–1.60)	10/76 (13.16)	1.28 (0.67–2.45)	46/330 (13.94)	1.41 (1.00–1.98)

All HRs and ORs adjusted for age, sex, hypertension, diabetes, coronary heart disease, atrial fibrillation, current smoking, total cholesterol level, NIHSS score, and mRS on admission. ACR, albumin-creatinine ratio; eGFR_{cys}, cystatin C-based estimated glomerular filtration; CVD, cerebrovascular disease.

stroke disability compared with the reference group. The interaction *p* value for eGFR_{cys} and ACR with poststroke disability event was not significant.

Combined Associations of eGFR_{cys} and ACR with Recurrent Stroke and CVD Composite Event

We also estimated the combined effects of baseline eGFR_{cys} and urine ACR on the risk for recurrent stroke and CVD events. As shown in Table 4, only in the category of ACR ≥30 mg/g, risks of recurrent stroke in those with eGFR_{cys} 60–119 mL/min/1.73 m² were higher compared with reference group of eGFR_{cys} 90–119 mL/min/1.73 m² and ACR <10 mg/g. Similarly, HRs for CVD composite event were significantly increased in all eGFR_{cys} category except for eGFR_{cys} of ≥120 mL/min/1.73 m² with an ACR ≥30 mg/g. The interaction *p* value for ACR and eGFR_{cys} with recurrent stroke and CVD composite event was 0.998 and 0.980, respectively.

Discussion

This is the first large study to explore the independent and combined effect of eGFR_{cys} and albuminuria in the post-acute ischemic stroke population. There are two main findings in the present study. Firstly, both reduced eGFR_{cys} and increased ACR were associated with higher risk of all-cause death and poststroke disability independently from each other and traditional cerebrovascular risk factors. Secondly, risks for all-cause mortality and poststroke disability increased in patients with both elevated albuminuria and reduced eGFR_{cys}, even at levels not reach the current cutoff of CKD, and the risks were at the highest in those with markedly elevated albuminuria and reduced eGFR_{cys}.

Previous reports evaluating the relationship between eGFR_{cr} and clinical outcomes after acute ischemic stroke have yielded conflicting results. Two small-scale studies

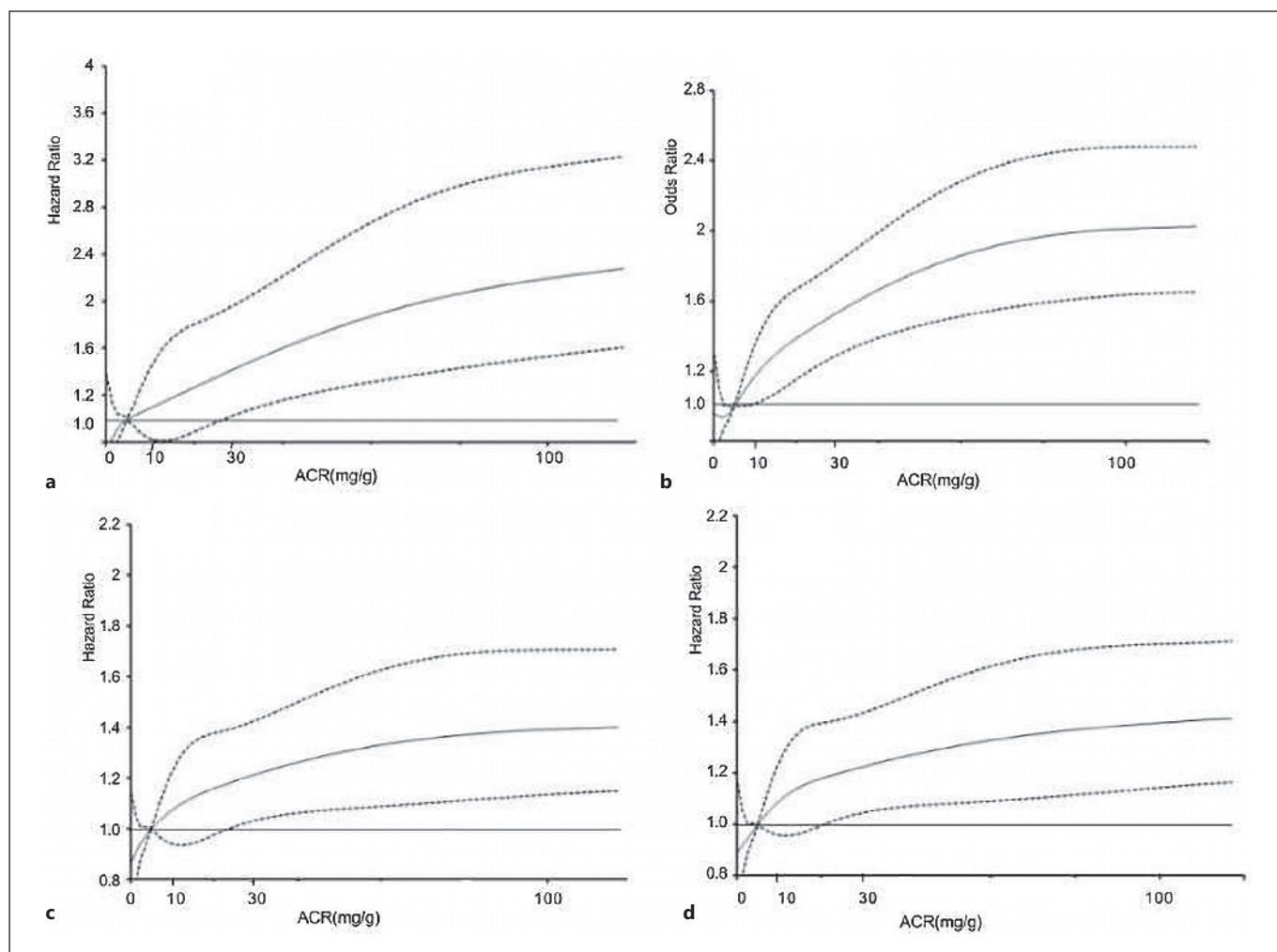


Fig. 2. HRs with 95% confidence intervals of urine ACR with the all-cause mortality (a), recurrence of stroke (c), CVD composite events (d), and ORs with 95% confidence intervals of ACR with the poststroke disability (b). Reference group is ACR <10 mg/g.

demonstrated that albuminuria, but not eGFR, was significantly associated with major vascular events, disability or mortality after stroke [1, 2]. In contrast, two large-scale studies demonstrated that low eGFR was significantly associated with in-hospital death and at-discharge death/disability, but without the albuminuria adjusted in the multivariate model [6, 7]. Estimates of eGFR_{cr} are routinely used; however, they may potentially lead to the overdiagnosis of CKD. Cystatin C is considered to be a potential alternative to serum creatinine for estimating GFR. In studies of prognosis, it has been consistently shown to be a better marker than creatinine, and eGFR_{cys} could be used as a confirmatory test for an adverse prognosis in patients with CKD [16, 21]. In the present study,

we observed significant correlation between eGFR_{cys} and poor outcomes after additional adjustment for albuminuria. It should be noted that all the above studies were focused on in-hospital poor outcomes, but our study was followed up for 1 year. In addition, our previous work based on CNSR-III showed that, compared with eGFR based on formulas calculated by the measurement of either creatinine (eGFR_{cr}), or creatinine in combination with cystatin C (eGFR_{com}), eGFR_{cys} may identify more patients at high risk of adverse outcomes after stroke/TIA (unpublished data). Therefore, in the present study, we selected cystatin C as the renal filtration marker to further classify the population into five renal function groups.

In the present study, 23.9% of the participants had $\text{ACR} \geq 30 \text{ mg/g}$ while 17.6% had $\text{eGFR}_{\text{cys}} < 60 \text{ mL/min/1.73 m}^2$. Furthermore, ACR have more effect than eGFR_{cys} on the poor outcomes including recurrent stroke and CVD composite event. It has been postulated that albuminuria and reduced renal filtration function may contribute to poor prognosis of stroke through different pathophysiological mechanisms [1]. Reduced GFR is suggested to represent the renal manifestations of systemic atherosclerosis [22, 23], whereas albuminuria may indicate a generalized systemic vasculopathy [24, 25] and endothelial dysfunction [26, 27]. However, the risks for all-cause death and stroke disability increased multiplicatively when the two biomarkers of renal function were combined, even when both markers were mildly abnormal with eGFR_{cys} of 60–89 mL/min/1.73 m² and ACR of 10–29 mg/g. In addition, although $\text{eGFR}_{\text{cys}} \geq 120 \text{ mL/min/1.73 m}^2$ alone was not associated with any adverse outcomes, higher risks of all-cause death and poststroke disability were observed in the subgroup with both $\text{ACR} \geq 30 \text{ mg/g}$ and $\text{eGFR}_{\text{cys}} \geq 120 \text{ mL/min/1.73 m}^2$. The hypothesized mechanism is hyperfiltration due to diabetes and higher BMI, but exact mechanism remains unclear and further investigation is needed in the future. Nonetheless, combined detection of these two markers may have more advantage in clinical practice.

In the present study, the majority of patients enrolled had $\text{ACR} < 10 \text{ mg/g}$, and thus participants were categorized into 3 categories based on ACR level: < 10 , 10–29, and $\geq 30 \text{ mg/g}$. The high-normal urine ACR level of 10–29 mg/g, lower than current definitions of albuminuria of 30 mg/g recommended by the KDIGO clinical practice guideline [28], was associated with a 19% and 16% higher risk of CVD composite event and poststroke disability compared to the referent group of $\text{ACR} < 10 \text{ mg/g}$. Consistent with our results, albuminuria at levels of 10–29 mg/g is associated with greater risk of cardiovascular events, deaths, and heart failure in general population [11, 12, 29]. However, the level of albuminuria in previous studies evaluating relationship between ACR and stroke outcome is higher than 30 mg/g [1–5]. Therefore, there is a need to place more resources in the screening and intervention of high-normal albuminuria among the stroke population.

The strengths of this study include the large scale and prospective population-based cohort and the central laboratory assay of serum cystatin C and urine ACR. Furthermore, multiple other vascular risk factors were well characterized, which allow for assessment of the independent relationship between the two renal bio-

markers and poor outcome. On the other hand, some limitations in the present study were identified. Firstly, the number of patients with severe renal impairment ($\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ or $\text{ACR} > 30 \text{ mg/g}$) was relatively small. Secondly, baseline serum cystatin C and urine ACR were measured only once. The day-to-day variability of ACR within individuals is high, such that a single sample may not accurately characterize the true level of albumin excretion. However, the large sample size and the central laboratory assay of serum cystatin C and urine ACR were the strengths of our study, thus the variance may be attenuated. In the future, multiple measurements of these markers are needed to reduce variability. Thirdly, subjects with absence of urine ACR or serum cystatin C data were not included in this study. The excluded patients were those with higher mRS on admission (1.94 ± 1.38 vs 1.89 ± 1.40 , $p = 0.03$), the selection bias may not be excluded (online supplemental; see www.karger.com/doi/10.1159/000522140 for all online suppl. material).

In conclusion, we found a significant association between urinary albumin excretion combined with diminished eGFR_{cys} at baseline and subsequent all-cause mortality and poststroke disability in patients with acute ischemic stroke. In the future, larger studies with multiple measurements of eGFR_{cys} and ACR are needed to verify these renal markers for risk assessment in stroke patients.

Statement of Ethics

The protocol of the CNSR-III study was approved by the Ethics Committee at Beijing Tiantan Hospital (IRB approval number: KY2015-001-01) and all participating centres. Written informed consent was signed by patients or their legally authorized representatives.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yongjun Wang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yongjun Wang, Yilun Zhou, and Yu Wu. Supplying patients: Xia Meng and Jinxi Lin. Drafting of the manuscript: Yilun Zhou and Yu Wu. Critical revision of the manuscript for important intellectual content: Yongjun Wang and Yilun Zhou. Statistical analysis: Yuesong Pan, Hao Li,

and Hongyi Yan. Study supervision and organisation of the project: Yongjun Wang, Xia Meng, Jinxi Lin, Hong Wang, and Kunihiro Matsushita.

Data Availability Statement

The data that support the findings of this study are openly available in at <http://creativecommons.org/licenses/by-nc/4.0/>.

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