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Higher plasma renin activity is associated with increased kidney damage risk in patients with hypertension and glucose metabolic disorders

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Abstract

The impact of renin on kidney remain unclear among hypertensives with glucose metabolic disorders (GMD). We aimed to evaluate the association between plasma renin activity (PRA) and kidney damage in hypertensive patients with GMD. Overall, 2033 inpatients with hypertension and GMD free of chronic kidney disease (CKD) at baseline were included. CKD was defined using estimated glomerular filtration rate (eGFR) and urine protein. PRA was treated as continuous variable, and also dichotomized as high ($\geq$0.65) or low (< 0.65) groups. The association of PRA with incident CKD was evaluated using multivariable Cox model controlling for antihypertensive medications and baseline aldosterone, and traditional parameters. Subgroup and interaction analyses were performed to evaluate heterogeneity. During a median follow-up of 31 months, 291 participants developed CKD. The incidence was higher in high-renin group than that in low-renin group (54.6 vs 36.6/1000 person-years). Significant association was observed between PRA and incident CKD, and the association was mainly driven by an increased risk for proteinuria. Each standard deviation increment in log-transformed PRA was associated with 16.7% increased risk of proteinuria (hazard ratio = 1.167, P = .03); compared with low-renin group, there was 78.4% increased risk for high-renin group (hazard ratio = 1.784, P = .001). Nonlinear associations were observed between PRA and kidney damage. Higher PRA is associated with greater risk of incident kidney damage, especially for positive proteinuria, in patients with coexistence of hypertension and diabetes, independent of aldosterone. In this patient population with high risk for kidney damage, PRA may serve as an important predictor.

KEYWORDS
chronic kidney disease, diabetes, hypertension, renin, risk factors

1 | INTRODUCTION

Chronic kidney disease (CKD) has been recognized as a major public health issue due to high prevalence and its strong association with cardiovascular events and premature death.[1] Incidence and prevalence of CKD have been increasing largely due to an ongoing epidemic of hypertension and glucose metabolic disorders (GMD).[2] Our previous study showed that prevalence of kidney dysfunction in hypertensive diabetic patients is higher than in those with either hypertension or diabetes mellitus (DM) alone,[3] suggesting higher risk for CKD in patients with coexistent hypertension and DM.

Hypertension and GMD often coexist due to common risk factors and overlapping pathophysiological processes, such as over activation of renin-angiotensin-aldosterone system (RAAS).[4,5] Evidences suggest that renin is an important mediator for vascular and organ damage.[6] By binding to its receptor, renin mediates an increase in angiotensin II (Ang II) and aldosterone, and induces a series of intracellular signaling pathways in cardiomyocytes, vascular, and renal cells, resulting in tissue and organ damage.[7] In addition, renin has also been demonstrated as an Ang II-independent profibrotic factor.[8]

Plasma renin has been associated with cardiovascular mortality in clinical studies.[9–11] However, conflicting evidence remains between plasma renin activity (PRA) and the development of CKD. John and colleagues reported in a cross-sectional study that higher PRA is associated with greater rates of CKD in population of primarily hypertensive patients.[12] Another case-control study with relatively small sample of high-risk population suggested a positive but marginal significant association between PRA and renal impairment.[13] On the contrary, longitudinal results from the Ohasama study showed a negative association that lower PRA is associated with the development of CKD in general Japanese population.[14] The most probable explanation for the variation in results is the different populations under observation. Previous studies mainly focused on patients with coronary heart disease or heart failure, and evaluated the association of PRA with cardiac events and all-cause mortality.[15,16] Few studies have focused specifically on patients with both hypertension and GMD, who have been proven to have excessive activation of RAAS and higher risk of kidney damage.[17] In addition, results may be biased by insufficient adjustment for confounding factors, such as aldosterone, which has recently been shown to be independently associated with incident CKD in hypertensive patients with GMD.[18] Therefore, the independently predictive value of PRA for kidney damage needs further validation.

To this aim, we evaluated whether PRA is independently associated with incident CKD in hypertensive patients with GMD, even after eliminating the confounding effects of aldosterone.

2 | METHOD

2.1 | Study population

Participants in this retrospective study were inpatients from Hypertension Center of People's Hospital of Xinjiang Uygur Autonomous
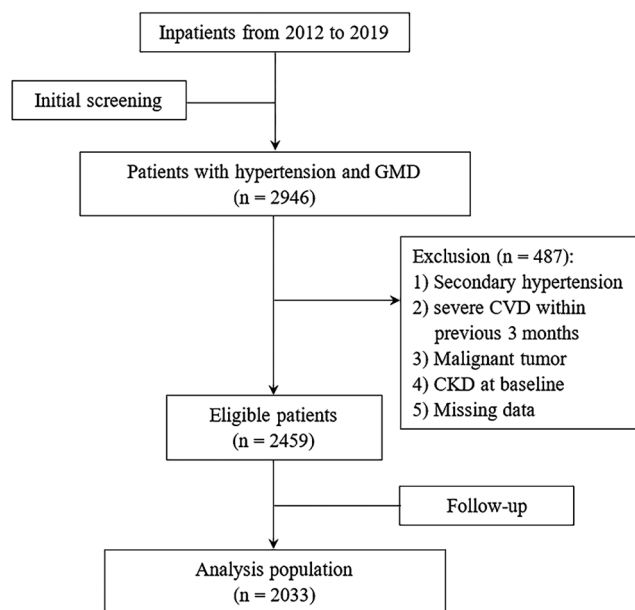

FIGURE 1 Flow diagram of patient enrollment. GMD, glucose metabolic disorders; CVD, cardiovascular disease; CKD, chronic kidney disease

Region between January 2012 and May 2019. As shown in Figure 1, in the initial screening, 2946 individuals aged 18 years or older, with hypertension and GMD and who have available PRA data were identified. Exclusion criteria were diagnosed secondary hypertension (primary aldosteronism, adrenal tumor, renal hypertension, Cushing syndrome, pheochromocytoma, and polycystic ovary syndrome), history of cardiovascular events within last 3 months (including myocardial infarction, heart failure, stroke, unstable angina, coronary revascularization, and coronary bypass operation), or malignant tumor. Individuals with CKD at baseline (n = 410) or missing baseline data (n = 77) were also excluded. Therefore, a total of 2459 participants were followed up for the interest of outcomes. The present study was approved by Ethics Committee at People's Hospital of Xinjiang Uygur Autonomous Region. All participants or their legal representatives signed written consent forms.

2.2 | Data collection and definition of diseases

We collected baseline information on age, sex, body mass index (BMI), blood pressure (BP), ethnicity, cigarette consumption, alcohol intake, duration of hypertension, types of GMD, use of antihypertensive and hypoglycemic medication. Laboratory analysis included fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), uric acid (UA), serum creatinine (Scr), serum potassium (K^+). The initial seated blood pressure during hospitalization was measured in the upper arm after patients rested quietly for 10 minutes at least with a mercury sphygmomanometer using international recommendations.[19]

The mean value of two measurements was recorded and used for analysis.

Hypertension was defined as systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg, or under antihypertensive therapy. GMD included pre-DM and DM. Pre-DM was defined as FPG ranged from 6.1 to < 7.0 mmol/L or 2-hour glucose ranged from 7.8 to < 11.0 mmol/L; DM was defined if there was a previous confirmed diagnosis, or FPG was ≥7.0 mmol/L, or 2-hour glucose was ≥11.1 mmol/L.

2.3 | Measurements of PRA and plasma aldosterone concentration (PAC)

Blood samples were collected under standardized conditions. That is, interfering drugs, including angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB), dihydropyridine calcium channel antagonist (CCB), β-blocker, diuretic, and aldosterone antagonist, were withdrawn for 4–6 weeks or replaced with slow-release verapamil and/or α1-adrenergic antagonists to minimize interference with measurements, as described in previous studies from the Center.[20] Fasting blood samples were collected in sitting posture between 08:00 am and 11:00 am after patients had been ambulant for at least 2 hours and seated for 15 minutes. PRA was measured using a radioimmunoassay kit from Northern Biotechnology Institutes, and the intra- and interassay coefficients of variation were 9.2% and 12.5%, respectively. PAC was measured by radioimmunoassay using a commercially available kit (Beckman Coulter), and the intra- and interassay coefficients of variation were 4.3% and 9.2%, respectively.

2.4 | Follow-up and outcome

The outcome for the current study was a new-onset CKD and its components (DRF and positive proteinuria) during follow up. Follow-up data were obtained using annual health check-ups or hospital readmission. Examination time of 3 months or longer after baseline was considered to be a valid data. If a participant experienced the outcomes more than once during follow-up, only the first outcome was used for analysis. For those without CKD events during follow-up, the data of the last follow-up was included in the analysis.

CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or the presence of proteinuria. eGFR was calculated by the simplified modification of diet in renal disease (MDRD) equation on the basis of data from Chinese adults.[21] Decreased renal function (DRF) was defined as eGFR < 60 mL/min/1.73 m^2. Urine protein was determined using urine dipstick results, and a positive of proteinuria was defined as urine protein ≥1+.

2.5 | Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range) according to results of normality test, and compared between groups using Student t test or Mann–Whitney U test. Categorical variables are summarized as number and percentage and compared between groups using Pearson chi-square test. Cumulative incidence of CKD and its components was estimated using the Kaplan–Meier method and compared by log-rank test.

Based on univariable Cox analysis and least absolute shrinkage and selection operator (LASSO) regression, three Cox proportional hazard regression models were constructed to determine the independent predictive value of PRA for CKD, DRF, and proteinuria. Model 1 adjusted variables with $P < .1$ in univariable Cox analysis. Model 2 was a combination of univariable and LASSO regression. Model 3 adjusted for all included factors. Proportional hazards (PH) assumptions were tested by adding interaction terms between PRA and time to the Cox model, and the PH assumption was satisfied for the present study ($P > .05$ for interaction). There was a significant correlation between FPG and HbA1c ($r = 0.74$), so only the latter was selected for adjustment. PRA was log-transformed (log-PRA) due to skewed distribution, and was also dichotomized as high-renin (PRA ≥.65) or low-renin (PRA < 0.65) groups according to Laragh and Alderman criteria.[22-24] Hazard ratios (HR) for outcomes were calculated for each SD increment in log-PRA and for high-renin group (vs. low-renin group). It has been reported that subnormal PRA (< 0.65) indicated sodium-volume excess "V" hypertension, whereas values ≥0.65 indicated renin-angiotensin vasoconstriction excess "R" hypertension,[25] suggesting potential differences of pathophysiological mechanism. Therefore, we first used 0.65 as the cut-off value of PRA. In addition, to describe the shape of the association between PRA and incident renal damage, we used restricted cubic splines incorporated into the Cox models. Furthermore, interaction terms were introduced into multivariable model to evaluate whether the association between PRA and renal outcomes differed according to age (group by mean of 55 years), sex, GMD status (pre-DM or diagnosed DM), PAC (group by median of 13.6), use of ACEI/ARB, use of calcium channel blockers (CCB), use of beta-blockers, and use of diuretics. Two-sided $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and R version 4.0.3.

3 | RESULTS

3.1 | Baseline characteristics

A total of 2,033 participants with complete baseline and follow-up data were analyzed. Baseline characteristics and comparison between high- and low-renin groups were shown in Table 1. Of participants, mean age was 55 years, 56.5% were men, and 58.1% had diagnosed DM. Mean BP were 148/88 mmHg; FPG and HbA1c were 6.2 mmol/L and 6.9%, respectively. Baseline eGFR was 118 mL/min/1.73 m^2. Median PRA (interquartile range) was 1.36 (0.53-2.62). The majority of participants (97%) received antihypertensive medications from baseline.

During the total follow-up of 5951 person-years with a median follow-up of 31 (interquartile range: 18–51) months, 291 participants

TABLE 1 Baseline characteristics of study population

Characteristics	Overall (No. = 2033)	Low renin (No. = 627) PRA < 0.65	High renin (No. = 1406) PRA ≥0.65	P value
Age (year)	55.5 ± 11.1	58.0 ± 10.2	54.4 ± 11.2	<.001
Sex, men, no. (%)	1149 (56.5)	297 (47.4)	852 (60.6)	<.001
Ethnicity, no. (%)				
Han	1215 (59.8)	348 (55.5)	867 (61.7)	
Uyghur	532 (26.2)	187 (29.8)	345 (24.5)	.022
Others	286 (14.0)	92 (14.7)	194 (13.8)	
Body mass index (kg/m^2)	28.1 ± 3.9	27.7 ± 3.6	28.2 ± 4.0	.013
SBP (mmHg)	148.5 ± 21.2	147.7 ± 21.0	148.8 ± 21.3	.277
DBP (mmHg)	87.9 ± 14.8	86.1 ± 13.7	88.7 ± 15.2	<.001
Duration of HTN (year)	7.0 (2.0-12.0)	8.0 (3.0-14.0)	6.0 (2.0-12.0)	.008
FPG (mmol/L)	6.2 ± 2.3	6.0 ± 2.1	6.3 ± 2.3	.027
HbA1c (%)	6.9 ± 1.3	6.9 ± 1.3	6.9 ± 1.3	.686
Diabetes, no. (%)	1181 (58.1)	256 (56.8)	825 (58.7)	.423
Total cholesterol (mmol/L)	4.43 ± 1.10	4.33 ± 1.02	4.48 ± 1.13	.005
Triglyceride (mmol/L)	1.66 (1.23-2.38)	1.55 (1.11-2.17)	1.73 (1.28-2.50)	<.001
HDL-C (mmol/L)	0.97 ± 0.24	0.98 ± 0.22	0.97 ± 0.24	.721
LDL-C (mmol/L)	2.62 ± 0.96	2.62 ± 0.86	2.63 ± 0.86	.839
Smoker, no. (%)	592 (29.1)	148 (23.6)	444 (31.6)	<.001
Drinker, no. (%)	539 (26.5)	126 (20.1)	413 (29.4)	<.001
Blood urea nitrogen (mmol/L)	5.11 ± 1.40	4.93 ± 1.35	5.18 ± 1.42	<.001
Uric acid (μmol/L)	332.1 ± 85.3	316.0 ± 84.2	339.5 ± 84.8	<.001
Serum potassium (mmol/L)	3.68 ± 0.28	3.63 ± 0.29	3.70 ± 0.28	<.001
Serum creatinine (μmol/L)	66.0 ± 15.7	63.5 ± 14.8	67.2 ± 15.9	<.001
Baseline eGFR (ml/min/1.73^2)	118.2 ± 30.0	120.1 ± 30.7	117.3 ± 29.7	.057
PAC (ng/dL)	13.6 (11.6-19.8)	12.8 (11.1-16.9)	14.4 (11.8-21.0)	<.001
PRA (ng/mL/h)	1.36 (0.53-2.62)	0.39 (0.26-0.50)	2.11 (1.26-3.21)	<.001
Hypoglycemic therapy, no. (%)	1138 (56.0)	340 (54.2)	798 (56.8)	.289
Insulin use, no. (%)	314 (15.4)	105 (16.7)	209 (14.9)	.278
Anti-hypertensive agents, no. (%)				
ACEI/ARB	1175 (57.8)	276 (44.0)	899 (63.9)	<.001
CCB	1677 (82.5)	539 (86.0)	1138 (80.9)	.006
Beta-blocker	443 (21.8)	145 (23.1)	298 (21.2)	.330
Diuretics	716 (35.2)	293 (46.7)	423 (30.1)	<.001
Follow-up time (months)	30.8 (17.9-50.7)	31.8 (17.9-52.4)	30.3 (17.9-49.7)	.308

Data are presented as means ± standard deviation or median (interquartile range) or number (percentage). PRA, plasma renin activity; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, HbA1c, glycated hemoglobin; high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

experienced incident CKD, with an incidence of 48.9/1000 person-years. Follow-up time was comparable between those in the high- and low-renin groups. Incidence of CKD was higher in high-renin group (54.6/1000 person-years) than that in low-renin group (36.6/1000 person-years).

3.2 | Association of PRA with CKD

Kaplan–Meier curve showed that the cumulative incidence of CKD was significantly higher in high-renin group (Figure 2-A). In univariate Cox regression analysis, age, SBP, duration of hypertension, FPG,
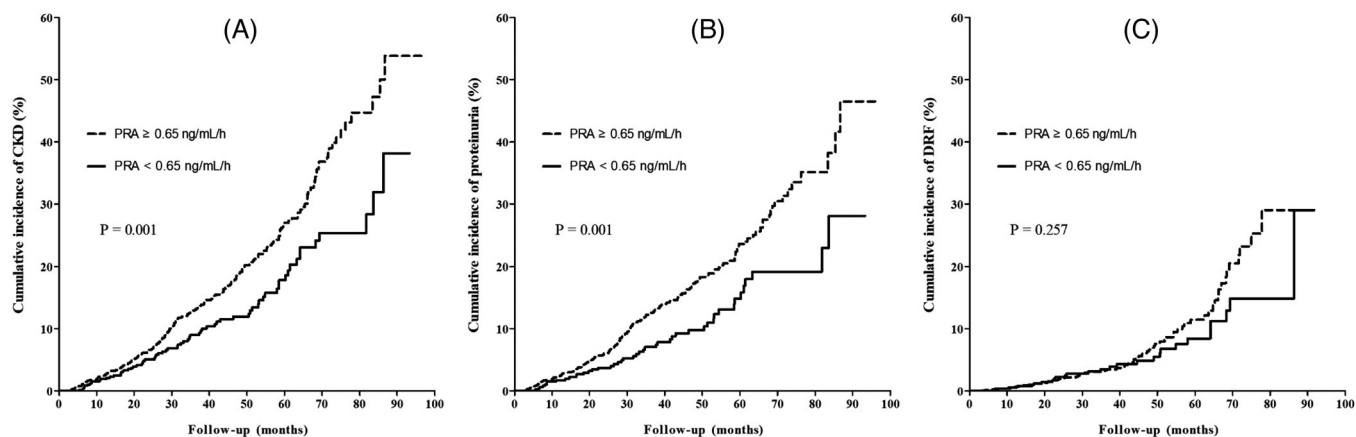
FIGURE 2 Kaplan–Meier curve of cumulative incidence of renal impairment based on high- and low-PRA. PRA, plasma renin activity; CKD, chronic kidney disease; DRF, decreased renal function. *P* value was generated based on log-rank test

HbA1c, DM, BUN, UA, K^+, PAC, PRA, hypoglycemia therapy, and anti-hypertensive medications were all significantly associated with incident CKD (Table 2). Accordingly, these factors except for FPG (due to the strong relation with HbA1c) were first included for adjustment and resulted in a significant association between PRA and incident CKD (Table 3-Model 1). Based on LASSO regression analysis, sex, ethnicity, alcohol intake, TC, HDL-C, and baseline eGFR were further introduced into Cox regression, and the association of PRA with CKD remained significant (Model 2). After adjusted for all parameters (Model 3), there was still independent and significant association between PRA and CKD, with 61.9% increased risk for CKD in high-renin group, and 14.4% increased risk in each SD increase of log-PRA.

3.3 | Association of PRA with proteinuria and DRF

Incidence of proteinuria events was 47.9/1000 person-years in high renin group and 28.6/1000 person-years in low-renin group. Consistent trend in cumulative incidence of proteinuria was also observed (Figure 2-B). Univariable analysis for incident proteinuria was shown in Table S1. In multivariate Cox regression analysis (Table 4), PRA was independently and significantly associated with incident proteinuria, after adjusting for factors derived from univariable analysis (Model 1) and LASSO regression (Model 2), and even after for all parameters (Model 3). Each SD increase in log-PRA caused 16.7% (*P* = .03) increased risk of proteinuria; compared with low-renin group, there was 78.4% increased risk for proteinuria in high-renin group. For the outcome of DRF, cumulative incidence was no significantly different between groups (Figure 2-C). Univariable (Table S2) and multivariable (Table 5) showed that there was no significant association between PRA and DRF.

3.4 | Additional analyses

Restricted cubic splines showed a nonlinear association between PRA and incident CKD (Figure 3-A). There was a positive dose-response relationship between PRA and incident CKD when PRA is less than

2.5, with a highest HR for the points of PRA ≈2.5. Although a downward trend was observed for CKD risk when PRA exceeds 2.5, the HR remains greater than 1. Similar results were found for outcomes of positive proteinuria (Figure 3-B). Given the nonlinear shape of the association between PRA and renal damage, we further analyzed the entire cohort according to tertiles and quartiles of PRA. Although a decrease in the HR was observed in the third and fourth groups compared with the second group, it remained significantly higher compared to the lowest PRA group (Table S3).

Above results indicated that the association of PRA with CKD was mainly driven by an increased risk for positive proteinuria. Therefore, we conducted subgroup and interactional analyses to further evaluate whether the association was homogeneous across the cohort. As shown in Figure 4, the association of PRA with incident proteinuria remained consistent in subgroup analyses by age, sex, and PAC. A strong association between PRA and higher risk of proteinuria was found in those with DM compared with those with pre-DM. The association of PRA and proteinuria was affected by taking ACEI/ARB or β-blockers. No interaction was found excepted for treatment with β-blockers (*P* for interaction = .041).

4 | DISCUSSION

These results extend and reinforce previous evidence to hypertensive diabetic patients that PRA is significantly and independently associated with incident kidney damage. The association between PRA and CKD is mainly driven by an increase in the risk for positive proteinuria but not decreased renal function. The increased risk of incident proteinuria associated with higher PRA is not changed by the adjustment for all factors including antihypertensive therapies and PAC, indicating the independently predictive value of PRA.

Renin is the initial and rate-limiting step of the RAAS and many experimental and clinical studies provide evidence that the RAAS is capable of stimulating atherosclerosis by triggering basic reactions, ultimately leading to growth, instability, and rupture of atherosclerotic plaques and facilitation of thrombosis.[26,27] It is well established

TABLE 2 Differences in characteristics between patients with and without CKD

Characteristics	Non-CKD (No. = 1742)	CKD (No. = 291)	Unadjusted HR	95% CI	P value
Age (year)	55.3 ± 11.0	56.9 ± 11.1	1.015	1.005-1.026	.005
Sex, men, no. (%)	989 (56.8)	160 (55.0)	0.927	0.736-1.169	.523
Ethnicity, no. (%)					
Han	1045 (60.0)	170 (58.4)		reference	
Uyghur	454 (26.1)	78 (26.8)	1.013	0.775-1.324	.925
Others	243 (13.9)	43 (14.8)	1.232	0.881-1.723	.223
Body mass index (kg/m^2)	28.0 ± 3.9	28.3 ± 2.9	1.019	0.990- 1.050	.203
SBP (mmHg)	148.0 ± 21.2	151.2 ± 21.0	1.011	1.006-1.016	<.001
DBP (mmHg)	87.7 ± 14.7	89.0 ± 15.3	1.005	0.997-1.013	.250
Duration of HTN (year)	6.0 (2.0-12.0)	9.0 (4.0-15.0)	1.025	1.012-1.038	<.001
FPG (mmol/L)	6.1 ± 2.2	6.6 ± 2.7	1.087	1.042-1.135	<.001
HbA1c (%)	6.9 ± 1.3	7.3 ± 1.5	1.207	1.126-1.293	<.001
Diabetes, no. (%)	981 (56.3)	91 (68.7)	1.881	1.467-2.411	<.001
Total cholesterol (mmol/L)	4.42 ± 1.10	4.49 ± 1.10	1.063	0.957-1.181	.253
Triglyceride (mmol/L)	1.63 (1.21-2.34)	1.81 (1.32-2.58)	1.010	0.946-1.077	.774
HDL-C (mmol/L)	0.98 ± 0.23	0.96 ± 0.24	0.665	0.395-1.122	.127
LDL-C (mmol/L)	2.62 ± 0.85	2.66 ± 0.89	1.048	0.911-1.205	.516
Smoker, no. (%)	515 (29.6)	77 (26.5)	0.877	0.675-1.138	.323
Drinker, no. (%)	473 (27.2)	66 (22.7)	0.820	0.623-1.079	.157
Blood urea nitrogen (mmol/L)	5.07 ± 1.38	5.29 ± 1.49	1.083	0.999-1.175	.054
Uric acid (μmol/L)	330.4 ± 85.0	343.5 ± 86.5	1.002	1.001-1.003	.001
Serum potassium (mmol/L)	3.68 ± 0.28	3.63 ± 0.30	0.552	0.380-0.801	.002
Serum creatinine (μmol/L)	65.6 ± 15.2	68.9 ± 18.3	1.004	0.997-1.010	.305
Baseline eGFR (mL/min/1.73 m^2)	119.0 ± 29.3	113.2 ± 33.3	0.998	0.994-1.002	.377
PAC (ng/dL)	13.5 (11.6-19.4)	15.3 (11.7-21.2)	1.031	1.019-1.043	<.001
PRA (ng/mL/h)	1.35 (0.51-2.60)	1.38 (0.71-2.78)	1.330[&]	1.047-1.689	.019
Hypoglycemic therapy, no. (%)	943 (54.1)	195 (67.0)	1.756	1.375-2.242	<.001
Anti-hypertensive agents, no. (%)					
ACEI/ARB	995 (57.1)	180 (61.9)	1.143	0.902-1.448	.367
CCB	1425 (81.8)	252 (86.6)	1.463	1.044-2.049	.027
Beta-blocker	384 (22.0)	59 (20.3)	0.958	0.719-1.274	.766
Diuretics	589 (33.8)	127 (43.6)	1.870	1.481-2.360	<.001

[&]Hazard ratio for Log-PRA. Data are presented as means ± standard deviation or median (interquartile range) or number (percentage). Results were derived from univariate Cox regression. CKD, chronic kidney disease; PRA, plasma renin activity; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

that excessive activation of RAAS induces organ damage mainly via increased Ang II and aldosterone.[7] However, residual risk of cardiovascular and kidney diseases remains, although blocking RAAS with ACEI/ARB has been shown to be reno-protective and widely used in antihypertensive therapy. The effect of renin (Ang II-independent) for augmenting profibrotic pathways has been proven,[8] which may be one of the explanations for our results. Experimental studies have demonstrated that renin inhibitor (aliskiren) attenuated inflammation and fibrosis in heart and kidney,[28] although other mechanism may be involved, such as suppressed aldosterone action via RAAS. In addition, insufficient use of ACEI/ARB may also be parts of the reasons for the results. There are nearly half of the participants not taking ACEI/ARB; and the association between PRA and kidney damage is significantly attenuated in ACEI/ARB subgroup. However, it is noteworthy that, compared with low-renin group, although not statistically significant, there is still 37% residual risk of incident proteinuria remaining in

TABLE 3 Association of the risk of CKD with PRA

Model	Covariates in model	Each SD increment in log-PRA			High PRA (vs low PRA)		
		HR	95% CI	P value	HR	95% CI	P value
1	Age, SBP, Duration of HTN, HbA1c, GMD type, BUN, UA, K$^+$, log-PAC, Hypoglycemic therapy, Anti-hypertensive agents	1.122	1.000-1.259	.050	1.562	1.175-2.078	.002
2	Model 1 + Sex, Ethnic, Drinking, TC, HDL-C, baseline eGFR	1.135	1.010-1.275	.033	1.604	1.203-2.138	.001
3	Model 2 + smoking, DBP, TG, LDL-C (Full-adjusted)	1.144	1.017-1.286	.025	1.619	1.213-2.160	.001

Results were derived from Cox proportional-hazards model. Model 1 included variables with $P < .1$ in univariate Cox analysis. Model 2 was a combination of univariate and LASSO regression. Model 3 adjusted for all factors. CKD, chronic kidney disease; PRA, plasma renin activity; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BUN, blood urea nitrogen; UA, uric acid; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

TABLE 4 Association of the risk of proteinuria with PRA

Model	Covariates in model	Each SD increment in log-PRA			High PRA (vs low PRA)		
		HR	95% CI	P value	HR	95% CI	P value
1	SBP, Duration of HTN, HbA1c, GMD type, BUN, UA, K$^+$, log-PAC, Hypoglycemic therapy, Anti-hypertensive agents	1.159	1.009-1.332	.037	1.741	1.230-2.464	.002
2	Model 1 + Age, Sex, Drinking, TC, HDL-C, Baseline eGFR,	1.169	1.018-1.343	.027	1.793	1.263-2.545	.001
3	Model 2 + Ethnicity, Smoking, DBP, TG, LDL-C (Full-adjusted)	1.167	1.015-1.341	.030	1.784	1.256-2.535	.001

Results were derived from Cox proportional-hazards model. Model 1 included variables with $P < .1$ in univariate Cox analysis. Model 2 was a combination of univariate and LASSO regression. Model 3 adjusted for all factors. SD, standard deviation; PRA, plasma renin activity; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BUN, blood urea nitrogen; UA, uric acid; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.

TABLE 5 Association of the risk of decreased renal function with PRA

Model	Covariates in model	Each SD increment in log-PRA			High PRA (vs low PRA)		
		HR	95% CI	P value	HR	95% CI	P value
1	Age, Ethnicity, SBP, Duration of HTN, HbA1c, GMD type, HDL-C, smoking, BUN, UA, baseline eGFR, log-PAC, Hypoglycemic therapy, Anti-hypertensive agents	1.041	0.853-1.269	.693	1.154	0.719-1.853	.553
2	Model 1 + Sex, Drinking, K$^+$	1.061	0.867-1.297	.566	1.198	0.739-1.943	.464
3	Model 2 + DBP, TC, TG, LDL-C (Full-adjusted)	1.046	0.850-1.287	.670	1.150	0.704-1.879	.576

Results were derived from Cox proportional-hazards model. Model 1 included variables with $P < .1$ in univariate Cox analysis. Model 2 was a combination of univariate and LASSO regression. Model 3 adjusted for all factors. SD, standard deviation; PRA, plasma renin activity; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; BUN, blood urea nitrogen; UA, uric acid; eGFR, estimated glomerular filtration rate; PAC, plasma aldosterone concentration; ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers.
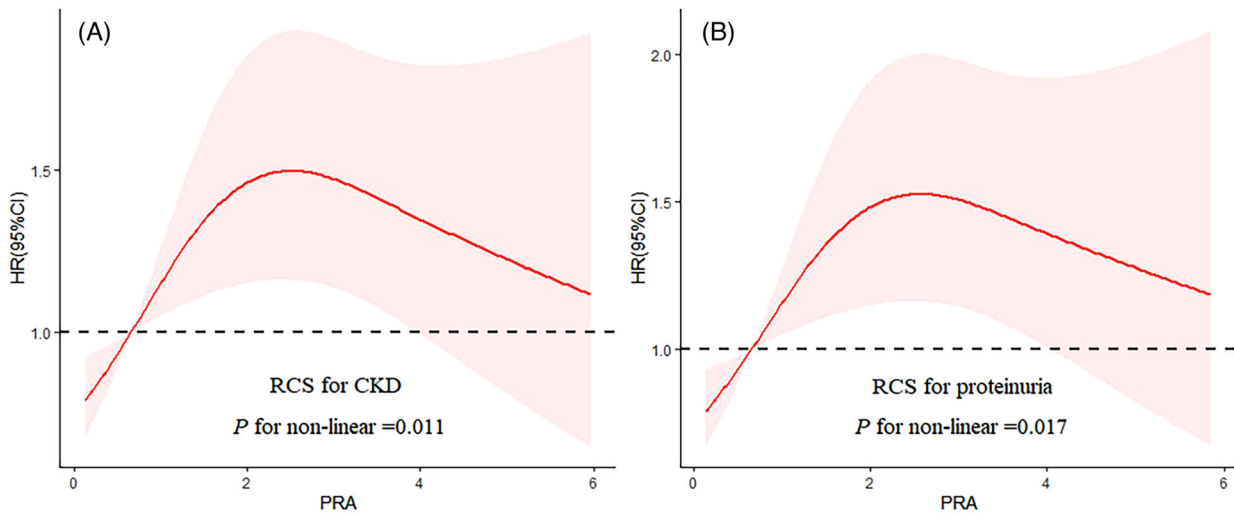
FIGURE 3 Restricted cubic splines for the shape of the association of PRA with CKD (A) and proteinuria (B). PRA, plasma renin activity; CKD, chronic kidney disease

Subgroup	No of participants	HR (95% CI)		P value	P-interaction
Age (year)					
≥55	872	1.615 (1.019-2.559)		0.041	0.987
< 55	768	1.996 (1.123-3.548)		0.019	
Sex					
Man	887	1.711 (1.063-2.755)		0.027	0.639
Women	753	1.819 (1.061-3.118)		0.030	
GMD					
Prediabetes	711	1.252 (0.671-2.334)		0.480	0.329
Diabetes	929	2.129 (1.372-3.304)		0.001	
ACEI/ARB					
Yes	942	1.370 (0.848-2.214)		0.199	0.205
No	698	2.447 (1.454-4.118)		0.001	
CCB					
Yes	1338	1.769 (1.219-2.567)		0.003	0.503
No	302	2.688 (0.870-8.307)		0.086	
β-blocker					
Yes	344	0.758 (0.361-1.591)		0.464	0.041
No	1296	2.200 (1.456-3.325)		< 0.001	
Diuretics					
Yes	559	2.257 (1.329-3.834)		0.003	0.465
No	1081	1.550 (0.958-2.507)		0.074	
PAC (ng/dL)					
< 13.6	834	1.820 (1.108-2.991)		0.018	0.942
≥13.6	806	1.822 (1.083-3.067)		0.024	

FIGURE 4 Stratification analysis on association between PRA and proteinuria. Results were derived from multivariate Cox regression and presented as hazard ratio for high PRA (compared with low PRA). Multivariate Model adjusted for Age, Sex, Drinking, SBP, Duration of HTN, HbA1c, GMD type, TC, HDL-C, Baseline eGFR, BUN, UA, K^+, Hypoglycemic therapy, Antihypertensive agents, and log-PAC. PRA, plasma renin activity; GMD, glucose metabolism disorders; PAC, plasma aldosterone concentration

high-renin group in patients who are already prescribed for ACEI/ARB. Similarly, results from LURIC study also showed a positive association between PRA and cardiovascular mortality in individuals under ACEI treatment.[10]

Several studies reported an association between PRA and kidney diseases in population of cardiovascular diseases with inconsistent results.[12–14,24] Our study suggests PRA as an independent predictor for future incident kidney damage, mainly for positive proteinuria, in hypertensive diabetic patients, who have higher risk for development of kidney disease. The results are compatible with interventional studies that aliskiren showed renoprotection by decreasing proteinuria or albuminuria, whereas had no effects for serum creatinine or eGFR.[29,30] Similarly, a recent study conducted in patients with essential hypertension using 0.65 as cut-off value revealed that higher PRA ($\geq$0.65), combined with high aldosterone-to-renin ratio (ARR), was associated with asymptomatic organ damage, such as higher carotid-femoral pulse wave velocity, central aortic pulse pressure, and lower estimated glomerular filtration rate.[24] Results from the SPYRAL HTN-OFF MED Pivotal trial also showed a different therapeutic response between high (PRA $\geq$0.65) and low (PRA < 0.65) groups, with a significant greater decrease in 24-hour and office systolic blood pressure after renal denervation for high PRA group.[22] In addition, a recent randomized controlled trial demonstrated that aliskiren restores endothelial function and induces a more prompt peripheral vasodilation in hypertensive and diabetic patients.[31] Therefore, in hypertensive diabetic patients with high renin (PRA $\geq$0.65), the primary prevention effects of direct renin inhibition on CKD deserves further explored.

Similar to previous studies that reported interaction between plasma renin concentration and use of β-blockers on cardiovascular death,[10] there is significant interaction term between PRA-related kidney damage and beta-blockers in the present study. Sever and colleagues also reported a greater effect of PRA on renal outcome when persons with β-blockers therapy were excluded.[13] It seems that use of β-blockers could attenuate the association of PRA with renal impairment. However, small sample size in the subgroup analysis restricted an accurate conclusion.

Although longitudinal design with large sample of high-risk population for CKD and reliable method for PRA measurement, several limitations warrant discussion. First, we failed to evaluate other therapy at baseline, such as lipid-lowering drugs; we also lacked 24-hour urinary sodium to evaluate the influence of dietary sodium intake on PRA. In addition, confounding of Ang II and other parameters, such as inflammatory factors, need to be considered in future studies. Second, serum creatinine and urinary protein were measured only one time, and proteinuria was examined through qualitative, but not quantitative methods. Third, the study was conducted in a single center, although conducted in a regional center for hypertension with patients of large age range and ethnic groups. Moreover, potential bias from undetected secondary hypertension limits the generalizability of the results. Fourth, the portion of lost to follow-up may potentially bias the results, although we combined rehospitalization and annual health check-up data for reducing the loss of follow-up rate. Finally, the observational design of the present study precludes the conclusion of direct cause-and-effect association between PRA and renal damage.

In conclusion, higher PRA is associated with greater risk of incident kidney damage, mainly for positive proteinuria, in hypertensive and diabetic patients, independent of antihypertensive medications and aldosterone. In this patient population with high risk for CKD, PRA may serve as an important predictor. For those with concomitant high PRA ($\geq$0.65), direct renin inhibition for CKD prevention may deserve further evaluated.

AUTHOR CONTRIBUTIONS

Mengyue Lin and Nanfang Li contributed to the study concept and design. Mengyue Lin, Jing Hong, Ting Wu, Zuhere Xiamili, Ling Tong, and Yue Lin contributed to data collection. Mengyue Lin, Mulalibieke Heizhati, and Lin Gan analyzed the data together and drafted the manuscript. All authors reviewed and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have declared that no conflict of interest exists.

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SUPPORTING INFORMATION

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