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ORIGINAL RESEARCH

The Renal Micro-Vasculopathy and Systemic Aldosterone-Renin Ratio (ARR) in Type 2 Diabetic Patients—A Retrospective Real-World Study

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Objective: To investigate whether the imbalanced aldosterone to renin ratio (ARR) is associated with renal micro-vasculopathy in type 2 diabetes mellitus (T2DM).

Materials and Methods: Data from 471 T2DM patients were retrospectively analyzed from 2019 to 2023. Blood samples were collected for hypertensive and diabetes-related parameters at the time of admission. The patients were divided into two groups based on laboratory measurement methods: plasma renin concentration or plasma renin activity.

Results: This study found that dividing patients into four quartiles showed significant increases in renal microvascular damage, measured by serum creatinine (SCr) and blood urea nitrogen (BUN), in contrast to the decline pattern of cystatin C (Cys) in the highest and lowest quartiles of ARR, respectively. This pattern contrasted with the levels of the urinary albumin-to-creatinine ratio (UACR) and the estimated glomerular filtration rate (eGFR). Correlation analysis identified gender, systolic blood pressure (SBP), and kidney function markers as significantly associated with ARR. Women exhibited the highest levels of renin or aldosterone. Furthermore, multilinear regression analysis in the PDC group indicated that ARR was independently influenced by insulin requirement, anti-hypertensive medication, serum magnesium, diastolic blood pressure (DBP), thyroid hormone, and calcium balance. In the PRA group, glucose metabolism, calcium homeostasis, and bile acids affect ARR change. The receiver operating characteristic (ROC) curve demonstrated that ARR could serve as a predictor of renal function and UACR.

Conclusion: The results indicated that the aberrant ARR was associated with renal glomerular injury. ARR can be employed to examine the relationship between renal injury and renin-angiotensin-aldosterone system (RAAS) activity.

Keywords: T2DM, ARR, renal function, eGFR, UACR

Introduction

Diabetic kidney disease (DKD) is a common subtype of microvascular complication, affecting about 30%-40% diabetic patients globally (T1DM: 30%, T2DM: 20%-50%).[1] According to a recent investigation based on the international disease database, the incidence of type 2 diabetic kidney disease was 2,501,248 cases in 2019, corresponding to an age-standardized incidence rate (ASIR) of 30.29 per 100,000 population, representing a 21.8% increase since 1990. The number of disability-adjusted years of life lost and survived (DALYs) attributed to DKD was 9,870.4 thousand, with an age-standardized rate of 120.2 per 100,000 population. This represents an 18.2% increase since 1990, and its associated mortality rate continues to increase with age, reaching its peak in the 60–79 age group and declining thereafter.[2] DKD is also one of the most prevalent causes of end-stage renal disease (ESRD), with a 5-year survival rate of less than 20% (for

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example, 25% in China) and increased long-term cardiovascular risks. Unsurprisingly, approximately one-third of T2D patients in China are suffering from DKD.[3,4] Hence, DKD was a primary public concern.

The lesion of GBM, and additionally, possibly with renal tubular involvement, results in gradually increased excretion of urinary albumin and a decline in renal filtration and absorption functions. The urinary albumin can serve as a critical indicator of DKD progression,[5,6] as renal impairment can be classified into stages I–V based on the urinary albumin to creatinine ratio (UACR) or urinary albumin excretion rate (UAE). The pathological stages of DKD can be categorized as follows: I—thickening of the renal basal membrane; II—glomerular mesangial expansion; III—tuberous sclerosis of the glomerulus (Kimmelstiel-Wilson or K-W nodules); IV—end-stage glomerular sclerosis.[7] Therefore, assessing renal function and proteinuria in T2DM, especially in high-risk patients, could be periodically performed to monitor the progression of DKD.

Currently, it is understood that a series of molecular changes and cellular or tissue injuries are the main pathophysiological features of DKD: 1) dysfunction of the glomerular basal filtration membrane (GBM) and glomerular podocytes,[8,9] 2) dysfunction of renal tubular epithelial cells,[10] 3) dysregulation of the expression and pathways of renal prorenin and its receptor or the renin-angiotensin-aldosterone system (RAAS),[11] 4) dyslipidemia,[12] 5) hypoxia and hemodynamic abnormalities,[13,14] 6) abnormal regulation of the ubiquitin proteasome system,[15] 7) disruption of nutrition-sensing signaling and activity,[16] among others. These changes may facilitate the development of diabetic nephropathy. Conversely, some risk factors can accelerate these processes: I) genetic factors;[17,18] II) hyperglycemia and its by-products, such as advanced glycation end products (AGEs);[19] III) risk factors like hyperuricemia and hypertension; IV) local factors including pro-/inflammatory cytokines,[20,21] transforming growth factor (TGF-β),[22] insulin-like growth factor-1 (IGF-1),[23] vascular endothelial growth factor (VEGF),[24] oxidative stress,[25] parathyroid hormone-related protein (PTHrP) and its receptor,[26] aging,[27] and toxins such as contrast agents,[28] among others.[29]

RAAS is vital for organ and vascular development throughout the patient's lifetime.[30,31] Its abnormal expression is linked to the onset of numerous metabolic disorders. According to Brownlee's research, the production of reactive oxygen species (ROS) may be increased by T2DM and hyperglycemia through RAAS activity.[32] Several metabolic factors, including obesity, hypertension, hyperglycemia, hypercortisolism, and medications (such as glucagon-like peptide-1 receptor agonist (GLP-1RA) and vitamin D), can potentially interfere with its activity. The final bio-activators of RAAS are aldosterone, and hyperaldosteronism has been shown to negatively impact cardiovascular safety. It is believed that activation of local RAAS leads to atherosclerosis, thrombosis, ischemia, tissue damage, and a higher incidence of acute myocardial infarction (AMI), stroke, nephropathy, cardiomyopathy, retinopathy, and neuropathy.[33,34] Our previous research examined the connections between systemic cardiovascu-lar disease and the retinal microvasculature.[35]

Plasma aldosterone levels may be elevated in primary hyperaldosteronism (PA).[36] The patient may present with hypokalemia and refractory hypertension, which is defined as blood pressure that remains uncontrolled despite the administration of three antihypertensive medications including diuretics.[37] Three causes of hyperaldosteronism are aldosterone-producing adenoma (35%), unilateral hyperplasia (2%), and idiopathic hyperaldosteronism (IHA, 60%).[38] Enhanced adrenal computed tomography imaging does not typically reveal distinct morphological changes in this condition. Measuring plasma renin and Ald levels, along with the Ald/renin ratio (ARR), is one of the most common methods used for PA screening before diagnosis. These laboratory results can support the diagnosis.[39] However, the definitive cutoff for ARR in idiopathic hyperaldosteronism varies due to differences in laboratory measurement methods.

Recent pathologic studies and clinical or pharmacological evidence have indicated that RAAS and abnormal aldosterone levels may be linked to organ damage, revascularization, fibrosis, or remodeling. Therapy targeting RAAS could slow the progression of diabetic complications, such as angiotensin receptor blockade (ARB),[40] mineralocorticoid receptor antagonists (MRAs) like Finerenone, which help reduce heart failure and diabetic renal microvascular issues,[41] and aldosterone synthase inhibitors, which may offer promising therapeutic potential in preventing mineral-induced renal damage.[42]

Because of the potential connection between renal impairment and its microvasculature, as well as hyperaldosteronism or a higher ARR, the link between the disorganized ARR and renal micro-vasculopathy in diabetic patients remains unclear. However, it is crucial to determine the ARR cutoff in DKD. Our study aimed to clarify the importance of ARR

in DKD and to develop a predictive marker for its progression. We also sought to anticipate the development of effective preventive strategies for T2DM patients with DKD.

Materials and Methods

Source of Patient Data

We gathered data from the inpatient record system at Shanghai Pudong Hospital on 471 adult patients with T2DM who were admitted between 2019 and 2023. Based on established World Health Organization (WHO) and American Diabetes Association (ADA) guidelines, they met the diagnostic criteria for T2DM and were enrolled randomly. Other types of diabetes, including T1DM, secondary diabetes, gestational diabetes, and other specific types, were not included in the criteria. A few severe conditions, such as diabetic acidosis, hyperosmolar hyperglycemic state, lactic acidosis, shock, hypoperfusion, severe systemic disorders, stroke, asthma, uremia, intestinal obstruction, and severe sepsis, were excluded from the study.

Blood Sampling and Methods of Laboratory Assessment

The metabolic and organic parameters were measured by collecting blood samples from patients the day after their admission. These included serum blood glucose, pancreatic islet function, hemoglobin A1C (HbA1C), electrolytes, thyroid function, liver and kidney function, as well as Ald, renin, and angiotensin levels. All biochemical indicators, including fasting blood glucose, liver function, and kidney function tests, were analyzed using a fully automatic biochemical analyzer (ADVIA Chemistry XPT, SIEMENS, USA). The three-month glycemic control was assessed by measuring HbA1C with a TOSOH G8 analyzer. C-peptide and thyroid function markers were tested using chemiluminescence methods on a fully automatic chemiluminescence immunoassay analyzer (ADAIVA Centaur XPT, SIEMENS, USA).

The ARR Cut-off Is Determined by Utilizing Two Distinct Patient Groups with a Variety of Renin Measurement Techniques

We evaluated the plasma aldosterone-to-renin ratio (ARR) in each patient. PDC is a direct measure of plasma renin concentration using the chemiluminescence assay, while PRA is an indirect measure of renin activity by assessing the production of Ang I with the radioimmunoassay method. Based on these different assays, patients were divided into two groups: PDC (n=210) and PRA (n=261). According to current diagnosis and treatment guidelines for PA, an enhanced CT scan was performed if the ARR value exceeded the cutoff (ARR cutoff: PDC: 57 (ng/mL/ng/mL); PRA: 300 (ng/L/μg/L*h)), in line with standards issued by the Chinese Endocrinology and Metabolism Association in 2022.

Statistical Analyses

The statistical analyses were performed using Prism (GraphPad, version 10.0) and SPSS (IBM, version 26.0). To compare different quartiles in PDC and PRA groups among patients with T2DM, all data were analyzed using either one-way ANOVA or Brown-Forsythe and Welch ANOVA tests, depending on whether the data met assumptions of normality and homogeneity of variances. In subsequent post-hoc analyses, the Dunnet T3 or Tukey's test was used. Spearman's nonparametric analysis was employed to assess correlations between ARR and related hormones. Multilinear regression analysis was conducted to identify independent variables associated with ARR in PDC and PRA. A p-value of <0.05 was considered statistically significant. Data are presented as the mean ± standard error of the mean (SEM).

Results

The Glucose Metabolic Status and Demographic Information of Patients Stratified by the Various Quartiles of ARR Through the PDC and PRA Measurement

Tables 1 and 2 shows the general and specific characteristics of patients in the PDC and PRA groups (Tables 1 and 2). To investigate how elevated ARR affects renal microvascular function, we divided ARR into four quartiles. To assess the demographic data, we examined hypertensive hormones (aldosterone, renin, angiotensin I, and II), glucose and metabolic indicators, hypertension status, medication history, and CT imaging across the four patient quartiles. Tables 3 and 4 detail these differences.

Table 1 The Metabolic Characteristics and Profile of the Hypertension Related Information of the Included Patients in Current Study

Variables	Value	Reference Range
Age	68.42±11.59	/
Bw (kg)	72.13±43.91	/
Gender (m/f)	233/238	/
HbA1c (%)	9.32±2.29	4.0–6.0
Hb (g/L)	127.09±20.27	130-175
GA (%)	24.81±9.13	11-17
FPG (mmol/L)	8.59±3.29	4.1–5.9
2hPPG (mmol/L)	14.53±5.17	<7.8
FPCP (nmo/L)	0.50±0.39	0.27–1.28
2hPPCP (nmo/L)	1.06±0.89	1.35–2.50
UACR (mg/gCr)	103.55±107.28	<30
Diabetes Duration	11.73±8.121	/
DM drug (naïve/insulin/OADS)	64/238/272	/
HT Duration	11.77±9.16	/
HT SBP (mmHg)	146.76±59.30	/
HT DBP (mmHg)	81.66±12.48	/
HT drug (Naïve/CCB/ACEI/ARB/Diuretics/α-blocker/β-blocker)	(55/246/11/247/150/9/39)	/

Table 2 The Information of the Included T2DM Patients on the Ald, Renin, Angiotensin, and ARR Based on the Different Renin Measurement

	Variables		Value	Reference Range
PDC (n=210)	Ald (pg/mL)		144.35±57.46	10-160
	Renin (pg/mL)		48.72±98.23	3.8–38.8
	ARR		12.27±12.23	/
	Ang I (ng/mL)		2.56±5.01	/
	Ang II (pg/mL)		99.65±31.61	/
	CT imaging of adrenal (n=203)	Numbers	178	/
		Unilateral hyperplasia	6	/
		Unilateral adenomatoid	12	/
		Bilateral hyperplasia	5	/
		Bilateral adenomatoid	2	/

(*Continued*)

Table 2 (Continued).

	Variables		Value	Reference Range
PRA (n=261)	Ald (ng/L)		155.18±33.80	59.5–173.9
	Renin (μg/L/h)		1.90±1.92	0.05–0.79
	ARR		154.06±100.76	/
	Ang I (μg/L)		2.52±2.70	/
	Ang II (ng/L)		108.99±111.78	/
	CT imaging of adrenal (n=215)	Numbers	183	/
		Unilateral hyperplasia	15	/
		Unilateral adenomatoid	12	/
		Bilateral hyperplasia	4	/
		Bilateral adenomatoid	1	/

Table 3 The Information of Demographic, Glucose Metabolic, Hypertension Related Markers, Drug History, CT Imaging of 4 Quartiles Patients According to the ARR Levels Assessed via PDC Method

Variables	Average	Quartile I	Quartile II	Quartile III	Quartile IV	P value
N (210)	/	51	53	53	52	/
Quartile range	/	0.23–3.56	3.56–8.70	8.70–16.00	16.00–57.79	/
Mean ARR	12.27±12.23	1.87±1.00	6.07±1.48	12.00±2.12	29.30±12.59	<0.0001
Mean Ald (pg/mL)	144.35±57.46	154.7±58.37	145.6±54.30	136.±49.50	141.8±67.08	0.447
Mean Renin (pg/mL)	48.72±98.23	145.±149.73	25.53±11.87	11.65±4.74	5.73±3.57	<0.0001
Ang I (ng/mL)	2.56±5.01	7.47±7.50	1.42±0.67	0.65±0.27	0.38±0.46	<0.0001
Ang II (pg/mL)	99.65±31.61	101.23±30.93	100.9±26.15	94.23±24.03	102.87±43.12	0.554
Age (y)	68.32±11.97	72.41±10.62	67.34±10.75	67.08±11.62	66.50±14.06	0.041
Bw (Kg)	70.41±13.40	70.49±17.37	71.46±12.01	72.14±11.48	67.34±11.96	0.268
Gender (m/f)	106/104	33/19	30/23	23/30	20/32	/
Diabetes Duration (y)	11.54±8.21	13.33±8.88	12.00±7.84	11.28±7.85	9.71±8.10	0.182
HbA1c (%)	9.37±2.31	9.68±2.47	9.25±2.43	9.41±1.91	9.19±2.44	0.795
GA (%)	24.48±8.81	27.69±9.81	23.87±8.74	23.76±7.56	23.56±8.93	0.183
FPG (mmol/L)	8.37±3.39	9.03±3.38	7.96±3.08	8.12±3.10	8.56±3.96	0.500
2hPPG (mmol/L)	14.93±5.23	15.15±5.67	13.87±4.85	14.54±4.27	16.14±5.78	0.215
FPCP (nmol/L)	0.52±0.42	0.53±0.31	0.50±0.48	0.46±0.33	0.60±0.53	0.412
2hPPCP (nmol/L)	1.11±1.00	1.04±0.91	1.19±1.12	0.91±0.78	1.20±0.99	0.484
UACR (mg/g)	111.1±108.57	80.00±82.81	125.13±123.79	128.48±110.75	111.07±109.28	0.121
HT Duration	11.78±10.02	12.12±7.22	13.37±13.44	9.68±8.75	11.60±9.15	0.270

(*Continued*)

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Table 3 (Continued).

Variables	Average	Quartile I	Quartile II	Quartile III	Quartile IV	P value
HT SBP (mmHg)	151.43±85.43	134.50±19.56	145.81±26.57	149.49±24.72	152.98±22.00	0.001
HT DBP (mmHg)	82.09±12.90	75.65±10.02	82.13±14.65	83.51±12.26	86.94±11.98	<0.0001
Drug Naïve	26	2	7	8	9	/
CCB (n)	101	22	25	27	27	/
ACEI (n)	4	0	2	0	2	/
ARB (n)	113	40	28	27	18	/
Diuretics (n)	67	26	14	14	13	/
α-blocker (n)	5	1	4	0	0	/
β-blocker (n)	11	3	0	3	5	
CT imaging (n=203)						
No adrenal neoplasm (n)	178	49	46	43	40	>0.05
Unilateral hyperplasia (n)	6	2	1	2	1	>0.05
Unilateral adenomatoid (n)	12	1	3	4	4	>0.05
Bilateral hyperplasia (n)	5	0	0	2	3	>0.05
Bilateral adenomatoid (n)	2	0	0	0	2	>0.05

Abbreviations: ARR, aldosterone to renin ratio; ald, aldosterone; Ang I, angiotensin I; Ang II, angiotensin II; Bw, bodyweight; m/f, male/ female; HbA1c, glycated hemoglobin A1c; GA, glycated albumin; FPG, fasting plasma glucose; 2hPPG, 2hrs postprandial plasma glucose; FPCP, fasting plasma C-peptide; 2hPPCP, 2hrs postprandial plasma postprandial C-peptide; UACR, urinary albumin to creatinine ratio; HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; α-blocker, α- adrenaline receptor blocker; β-blocker, β- adrenaline receptor blocker; CT, computed tomography imaging.

Table 4 The Information of Demographic, Glucose Metabolic, Hypertension Related Markers, Drug History, CT Imaging of 4 Quartiles Patients According to the ARR Levels Assessed via PRA Method

Variables	Average	Quartile I	Quartile II	Quartile III	Quartile IV	P value
N (261)	/	65	66	65	64	/
Quartile range	/	13.07–64.81	64.81–143.63	143.63–214.16	214.16–512.72	/
Mean ARR	154.06±100.76	38.35±13.95	107.23±24.20	181.10±21.48	286.8±61.82	<0.0001
Ald (ng/L)	155.18±33.80	158.88±37.94	151.71±37.65	147.61±27.73	162.78±29.40	0.049
Renin (μg/L/h)	1.90±1.92	4.71±1.87	1.50±0.57	0.82±0.18	0.59±0.14	<0.0001
Ang I (μg/L)	2.52±2.70	6.22±2.87	2.07±1.16	1.09±0.64	0.72±0.28	<0.0001
Ang II (ng/L)	108.99±111.78	213.24±182.93	89.45±40.76	68.54±19.66	65.39±12.78	<0.0001
Age (y)	68.51±11.31	66.43±14.12	68.62±11.87	69.83±9.73	69.06±8.75	0.35
Bw (Kg)	73.51±57.77	74.17±15.05	71.46±13.32	82.14±113.31	66.18±13.44	0.468
Gender (m/f)	127/134	43/22	32/34	27/38	25/40	/
Diabetes Duration	11.88±8.06	10.43±8.21	12.83±8.34	12.18±8.40	12.09±7.28	0.371

(*Continued*)

Table 4 (Continued).

Variables	Average	Quartile I	Quartile II	Quartile III	Quartile IV	P value
HbA1c (%)	9.27±2.28	9.58±2.09	9.57±2.77	9.19±2.17	8.77±1.96	0.126
GA (%)	25.03±9.36	26.54±8.72	26.40±11.54	24.41±8.69	22.78±7.70	0.067
FPG (mmol/L)	8.75±3.21	9.51±3.41	8.90±3.29	8.43±2.90	8.15±3.13	0.082
2hPPG (mmol/L)	14.17±5.11	14.35±5.18	14.39±5.39	14.19±5.32	13.75±4.62	0.934
FPCP (nmol/L)	0.48±0.36	0.58±0.43	0.44±0.31	0.49±0.42	0.41±0.25	0.32
2hPPCP (nmol/L)	1.02±0.81	1.06±0.79	1.01±1.02	1.01±0.67	1.01±0.73	0.988
UACR (mg/g)	95.01±105.51	92.98±99.19	91.25±102.96	106.93±118.02	86.72±101.52	0.841
HT Duration(y)	11.75±8.42	10.31±7.42	12.70±10.36	13.29±8.30	10.73±7.01	0.114
HT SBP (mmHg)	143±21.41	135.95±23.35	144.05±22.72	147.43±20.79	144.42±17.03	0.015
HT DBP (mmHg)	81.31±12.14	79.72±13.72	83.85±11.90	80.40±10.50	81.08±12.14	0.226
Drug Naïve	29	6	8	5	10	/
CCB (n)	145	32	32	41	40	/
ACEI (n)	7	4	1	1	1	/
ARB (n)	134	35	39	33	27	/
Diuretics (n)	83	26	24	17	16	/
α-blocker (n)	4	1	3	0	0	/
β-blocker (n)	28	10	5	5	8	/
CT imaging (n=215)						
No adrenal neoplasm (n)	183	46	43	46	48	>0.05
Unilateral hyperplasia (n)	15	3	4	3	5	>0.05
Unilateral adenomatoid (n)	12	2	2	3	5	>0.05
Bilateral hyperplasia (n)	4	0	2	2	0	>0.05
Bilateral adenomatoid (n)	1	0	0	1	0	>0.05

Abbreviations: ARR, aldosterone to renin ratio; ald, aldosterone; Ang I, angiotensin I; Ang II, angiotensin II; Bw, bodyweight; m/f, male/ female; HbA1c, glycated hemoglobin A1c; GA, glycated albumin; FPG, fasting plasma glucose; 2hPPG, 2hrs postprandial plasma glucose; FPCP, fasting plasma C-peptide; 2hPPCP, 2hrs postprandial plasma postprandial C-peptide; UACR, urinary albumin to creatinine ratio; HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; α-blocker, α- adrenaline receptor blocker; β-blocker, β- adrenaline receptor blocker; CT, computed tomography imaging.

The Effects of ARR Elevation on Microvascular Lesions in DM Patients, as Indicated by Glomerular Indices Such as eGFR, SCr, BUN, UA, and CYS

The renal glomerular lesion was subsequently analyzed across various ARR quartiles of PRA and PDC. The results showed that UACR and eGFR were lower, approaching the lower and upper limits of the ARR quartiles in both groups, with significance observed in PDC (quartile I vs quartile III: 72.71±23.82 mL/min*1.73m^2 vs 86.08±24.23 mL/min*1.73m^2, p=0.03). Similarly, the trends of SCr and BUN contrasted in a manner consistent with eGFR, with BUN showing significant differences in PDC (quartile I vs quartile II: 9.43±4.79 mmol/L vs 7.35±3.66 mmol/L, p=0.007; quartile I vs quartile III: 9.43±4.79 mmol/L vs 6.67 ±3.57 mmol/L, p=0.007), and SCr in PRA (quartile I vs quartile III: 85.22±31.68 μmol/L vs 69.58±26.07 μmol/L, p=0.02).

Regarding the renal lesion marker cystatin C, a declining trend was observed, with a significantly lower value noted in the fourth quartile of PRA (quartile I vs quartile IV: 1.23±0.59 mg/L vs 0.92±0.34 mg/L, p=0.049) (Figure 1).

The Significance of ARR Elevation on Microvascular Renal Damage in T2DM Patients, Indicated by Renal Tubular-Related Markers

In a more advanced stepwise analysis, we examined whether the increase in ARR has a specific effect on renal tubular lesion-related indicators. We observed declining trends in β2 microglobin (β2MG) and retinol-binding protein (RBP), while there were no consistent changes in α1 microglobin (α1MG) or N-acetyl-β-D-glucosidase (NAG) between PDC and PRA (Figure 2).

The Effects of Increased ARR Levels on Serum Electrolyte and Trace Element Concentrations in the PDC and PRA Groups

We examined the trend of changes in serum electrolytes, including sodium, potassium, and chlorine, as well as serum calcium, phosphorus, magnesium, and trace elements like serum iron, resulting from alterations in the interaction between hypertensive hormones and the homeostasis of electrolytes and trace elements. The serum sodium trend showed

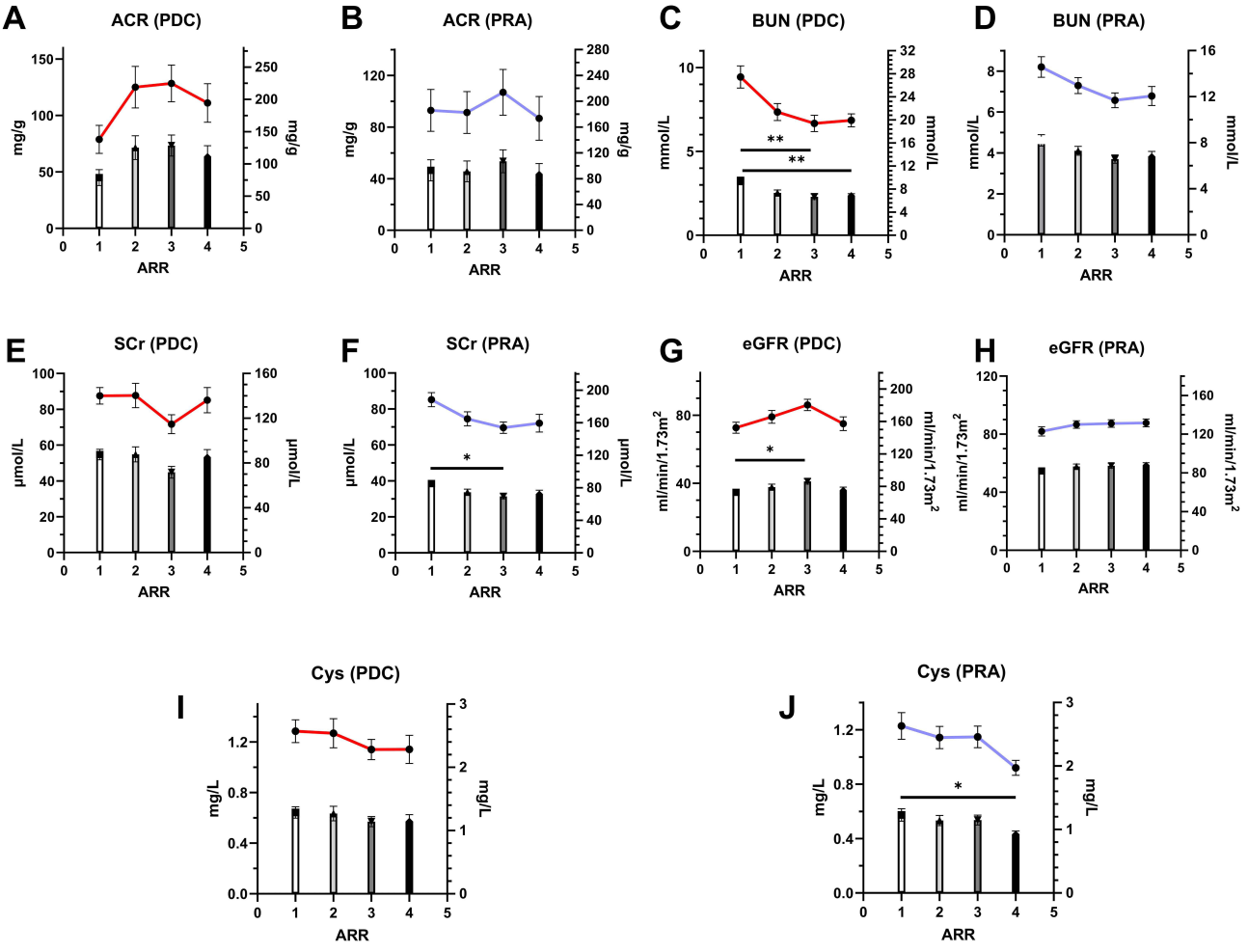

Figure 1 The trend of renal glomerular function related indices change: UACR (**A** and **B**), BUN (**C** and **D**), SCr (**E** and **F**), eGFR (**G** and **H**), Cys (**I** and **J**), in response to the elevation of ARR level in PDC and PRA.

Note: **: p<0.01; *: p<0.05.

Abbreviations: PDC, plasma direct renin concentration; PRA, plasma renin activity; ACR, urinary albumin to creatinine ratio; BUN, blood urea nitrogen; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; Cys, cystatin C.

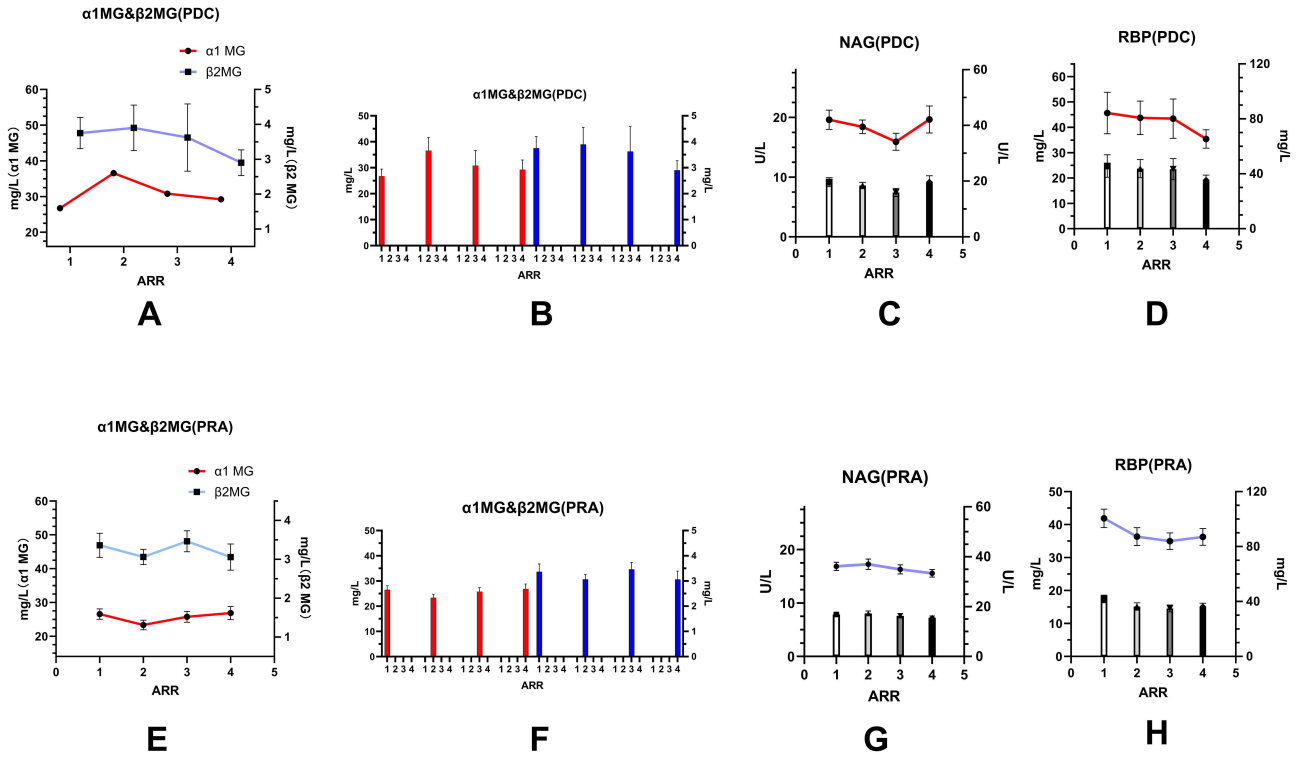

Figure 2 The trend of the renal tubular lesion related marker change: α1MG and β2MG (**A**, **B**, **E** and **F**), NAG (**C** and **G**), RBP (**D** and **H**), in response to the elevation of ARR level of PDC and PRA.
Abbreviations: β2MG, β2 micro-globin; α1MG, α1 micro-globin; RBP, retinol binding protein, NAG, N-acetyl-β-D-glucosidase.

an increase in quartiles II–III, with effects particularly evident in the PDC, where the difference between quartile I and quartile III was 138.73±6.03 mmol/L and 141.59±3.12 mmol/L, respectively (p=0.03). Unlike serum sodium, iron levels were significantly elevated in both quartiles I and IV, while they were relatively reduced in quartiles II and III in both PRA and PDC. Serum calcium showed a decline trend in PDC, whereas in PRA, calcium levels decreased, but not significantly in quartile IV. Levels of potassium and chlorine remained relatively stable despite changes in ARR. Conversely, phosphorus levels fluctuated inconsistently between PDC and PRA, but these changes were not statistically significant (Figure 3).

The Spearman Non-Parametric Correlation Analyses Between the ARR and Other Metabolic Markers in T2DM

Furthermore, we conducted analyses to explore the relationship between ARR and related parameters. The results indicated significant correlations between ARR and gender, SBP, BUN, SCr, and UA. ARR shows a positive correlation with SBP (PDC: r=0.27; p<0.0001; PRA: r=0.17; p=0.007), while it is negatively correlated with male gender (PDC: r=−0.219; p=0.001; PRA: r=−0.193; p=0.002; Male:2; female:1). Additionally, ARR is inversely related to BUN (PDC: p=0.001; PRA: p=0.001), SCr (PDC: p=0.033; PRA: p=0.002), and UA (PDC: p=0.030; PRA: p=0.00001) (Figure 4).

The Significance of Gender Variation on ARR and Its Components

We performed subgroup analyses to examine gender differences in ARR and related hypertensive hormones across the four quartile groups in both PDC and PRA, as previous correlational results showed that female gender was strongly associated with higher ARR levels. The analysis revealed that renin and ARR values were significantly higher in females, approaching the extremes of quartile I and IV groups, which represent the highest levels of renin or Ald (PDC: ARR: Quartile IV: female vs male: 31.39±13.92 vs 25.96±9.49, p=0.0119; PRA: renin: female vs male: 5.38±2.25μg/L*h vs

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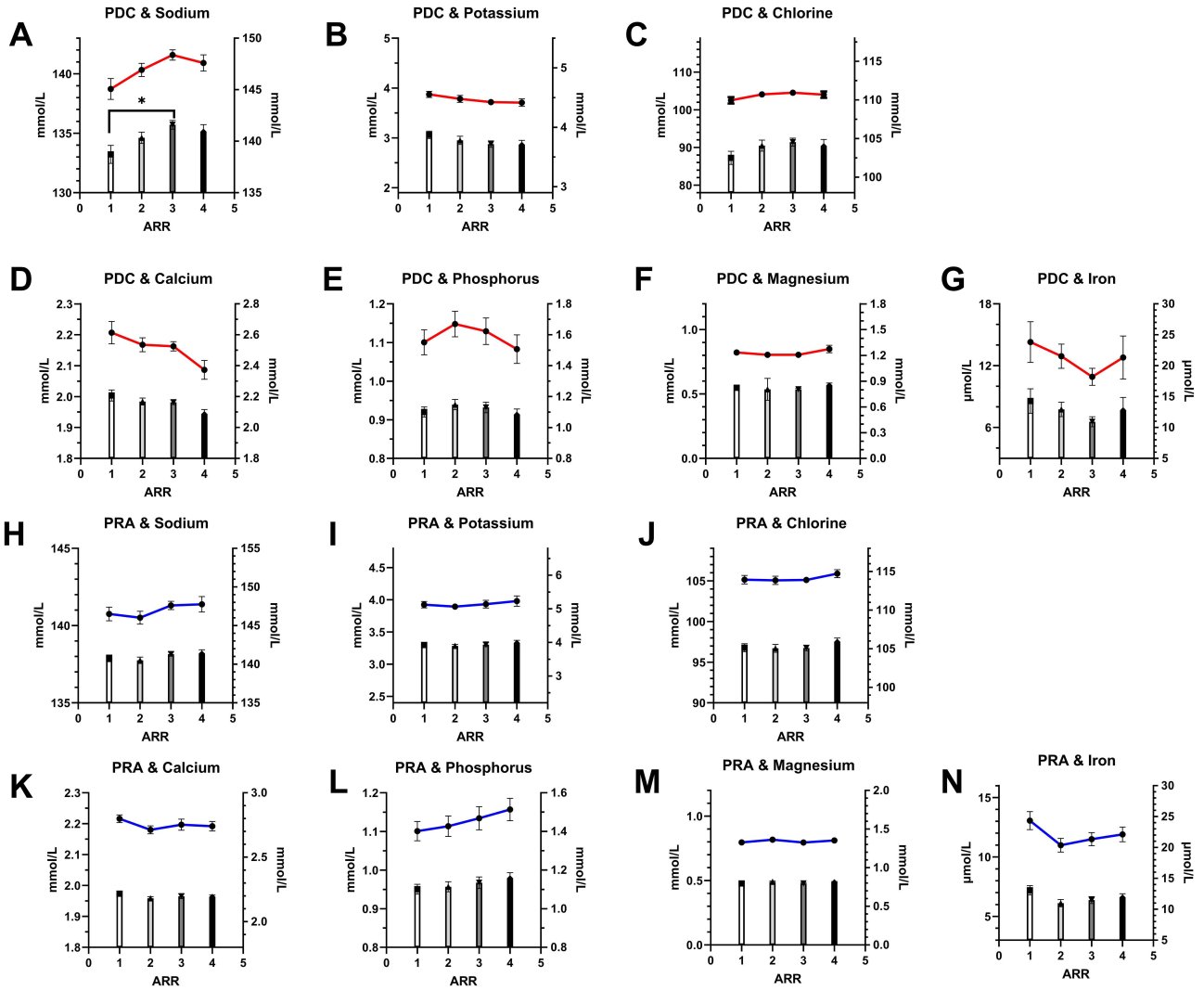

Figure 3 The trend of serum electrolyte, including sodium (**A** and **H**), potassium (**B** and **I**), chlorine (**C** and **J**), calcium (**D** and **K**), phosphorus (**E** and **L**), magnesium (**F** and **M**), as well as trace elements iron levels (**G** and **N**) change, in response to elevation of ARR levels.
Note: *: p< 0.05.
Abbreviations: PDC, plasma direct renin concentration; PRA, plasma renin activity.

4.36±1.57μg/L*h, p=0.0003). However, the increase in ARR in both PDC and PRA did not lead to significant changes in other hypertension-related hormones (Figure 5).

The Multilinear Regression Models of Changes in ARR via PDC or PRA

Furthermore, we conducted multilinear regression analyses to identify the key factors influencing the ARR change. The regression model for PDC included insulin administration, hypertension, gender differences, serum magnesium levels, diastolic blood pressure, hypertensive medications such as β-Blockers, ARB, free thyroxine (FT4), parathyroid hormone (PTH), and 25 OH Vitamin D as significant predictors (R square: 0.465) (Table 5). The PRA model was more dependent on changes in renin, aldosterone (Ald), Angiotensin I, fasting plasma glucose (FPG), uric acid (UA), phosphorus, PTH, and γ-GGT (R square: 0.607) (Table 6).

The Predictive Value of the ARR in PDC and PRA for Renal Glomerular Lesions Represented by eGFR, UACR via ROC

Finally, we generated the receiver operating characteristic (ROC) curve to evaluate the predictive value of ARR for glomerular lesions in both PRA and PDC. Our results showed that the ARR in the ROC curve for the PDC group had an

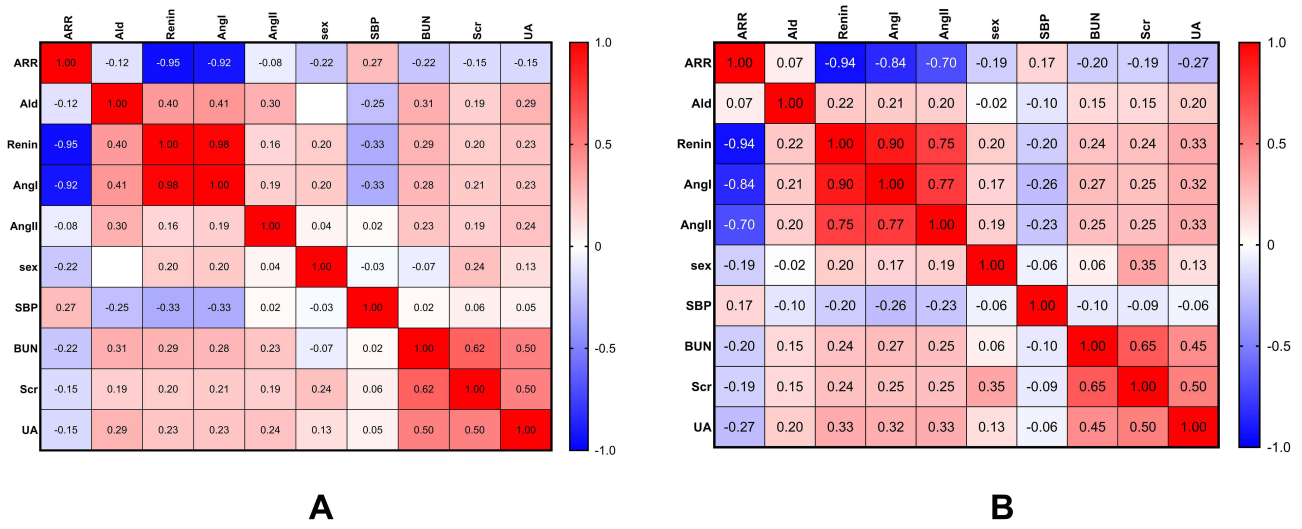

Figure 4 The heatmap reveals the Spearman nonparametric correlational analyses which shows relationship between the ARR and gender variation, SBP and renal glomerular function in PDC group (**A**) and PRA group (**B**).
Notes: The gradient degree in red represents the degree of positive correlation. In contrast, the gradient degree in blue represents the degree of negative correlation, as shown by the color bar on the right side of the map.

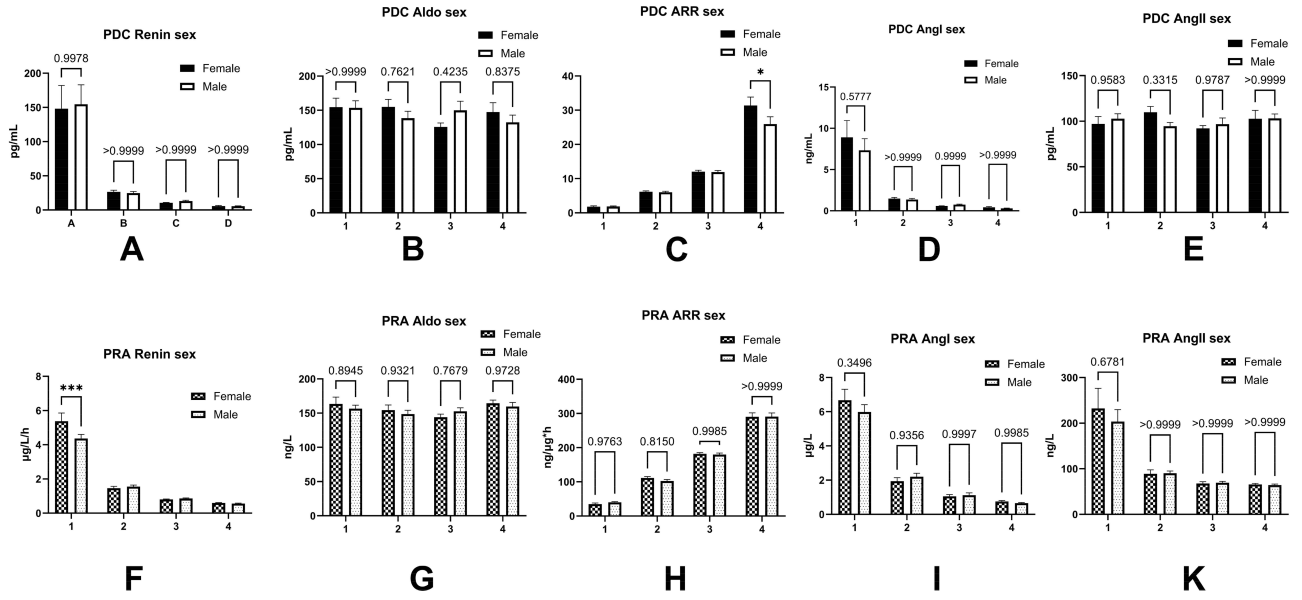

Figure 5 The subgroup analyses reveal the implications of gender variation on renin (**A** and **F**), ald (**B** and **G**), ARR (**C** and **H**), Ang I (**D** and **I**), Ang II (**E** and **K**).
Note: *: p<0.05; ***: p<0.001.
Abbreviations: PDC, plasma direct renin concentration; PRA, plasma renin activity; ald, aldosterone; ARR, aldosterone to renin ratio; Ang I angiotensin I; Ang II, angiotensin II.

area under the curve (AUC) of 98.35%, with a sensitivity of 94.74%, a specificity of 93.30%, a Youden index of 88.04%, and a optimal cutoff point of 36.60. In comparison, the PRA group had a sensitivity of 66.67% and a specificity of 67.05%, with a Youden index of 33.72% and an AUC of 69.40%. Regarding UACR, the AUC values for PDC and PRA were 93.94% and 70.85%, respectively. The sensitivity, specificity, Youden index, and cutoff for ARR in the PDC group were 90.91%, 98.30%, 89.21%, and 28.96, respectively. PRA showed values of 70.11%, 73.25%, 43.36%, and 80.24 ng/L/μg/L*h (Figure 6).

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Table 5 The Multilinear Regression Analysis Revealed the Independent Determinants to the ARR Change via PDC Methods

Multilinear Regress	R	0.682	R^2	0.465	Adjusted R^2	0.438	Tolerance	VIF
	Variables	B	SE	β	t	Sig		
	Constant	−4.434	9.954		−0.583	0.561		
	Renin	−0.027	0.007	−0.216	−3.885	<0.0001	0.873	1.145
	Insulin ad	−5.308	1.316	−0.217	−4.034	<0.0001	0.926	1.080
	Mg^{2+}	19.544	5.531	0.189	3.533	0.001	0.943	1.060
	DBP	0.202	0.052	0.213	3.909	<0.0001	0.907	1.102
	β-Blocker ad	11.709	2.889	0.214	4.053	<0.0001	0.967	1.034
	ARB ad	−6.067	1.410	−0.248	−4.304	<0.0001	0.811	1.233
	Gender	−6.236	1.361	−0.256	−4.581	<0.0001	0.865	1.156
	FT4	−0.445	0.182	−0.131	−2.438	0.016	0.938	1.066
	PTH	0.667	0.256	0.142	2.604	0.010	0.903	1.108
	25OH Vit D	0.159	0.078	0.111	2.027	0.044	0.899	1.113

Abbreviations: ad, administration; Mg, magnesium; DBP, diastolic blood pressure; β-blocker, β- adrenaline receptor blocker; ARB, angiotensin II receptor blocker; FT4, free thyroxine; PTH, parathyroid hormone; 25 OH Vit D, 25 hydroxy vitamin D.

Table 6 The Multilinear Regression Analysis Revealed the Independent Determinant to the ARR Change via PRA Methods

Multilinear Regress	R	0.779	R^2	0.607	Adjusted R^2	0.594	Tolerance	VIF
	Variables	B	SE	β	t	Sig		
	Constant	90.301	32.609		2.769	0.006		
	Renin	−27.340	4.548	−0.521	−6.012	<0.0001	0.208	4.815
	Ald	0.807	0.129	0.271	6.280	<0.0001	0.840	1.191
	Ang I	−7.690	3.284	−0.206	−2.342	0.020	0.202	4.948
	FPG	−2.894	1.343	−0.091	−2.155	0.032	0.868	1.152
	UA	−0.113	0.036	−0.139	−3.154	0.002	0.802	1.246
	Phosphorus	55.165	19.394	0.118	2.844	0.005	0.905	1.105
	PTH	2.965	1.251	0.099	2.370	0.019	0.899	1.112
	γ-GGT	−0.133	0.062	−0.085	−2.137	0.034	0.980	1.020

Abbreviations: Ald, aldosterone; Ang I, angiotensin I; FPG, fasting plasma glucose; UA, uric acid; PTH, parathyroid hormone; γ-GGT, γ-glutamyl transferase.

Discussion

Currently, DKD is a common complication in T2DM that causes a range of health issues and burdens on populations worldwide. Although many critical molecules, pathways, and pathological mechanisms have been identified, the trend toward ESRD progression remains highly concerning. The variable nature of proteinuria, which leads to a distinct decline in renal function among diabetic patients, is one of the main factors driving this phenomenon. We retrospectively analyzed the relationship between ARR and renal lesions using various methods, such as PRA or PDC. Based on the ARR value, we reclassified patients into four quartiles and examined its impact on renal function and the progression of DKD.

Initially, and most importantly, we compared the demographic data and ARR distribution in each quartile of the PDC and PRA groups. The results showed that plasma renin levels significantly decreased with an increase in ARR, while Ald did not. This suggests that renin is more sensitive to changes in ARR. We found a significant difference in blood pressure among the four quartiles in the PDC and PRA groups, especially SBP. The differences between quartiles may be linked to changes in ARR-related hormones, which could explain variations in antihypertensive drug use. We also observed

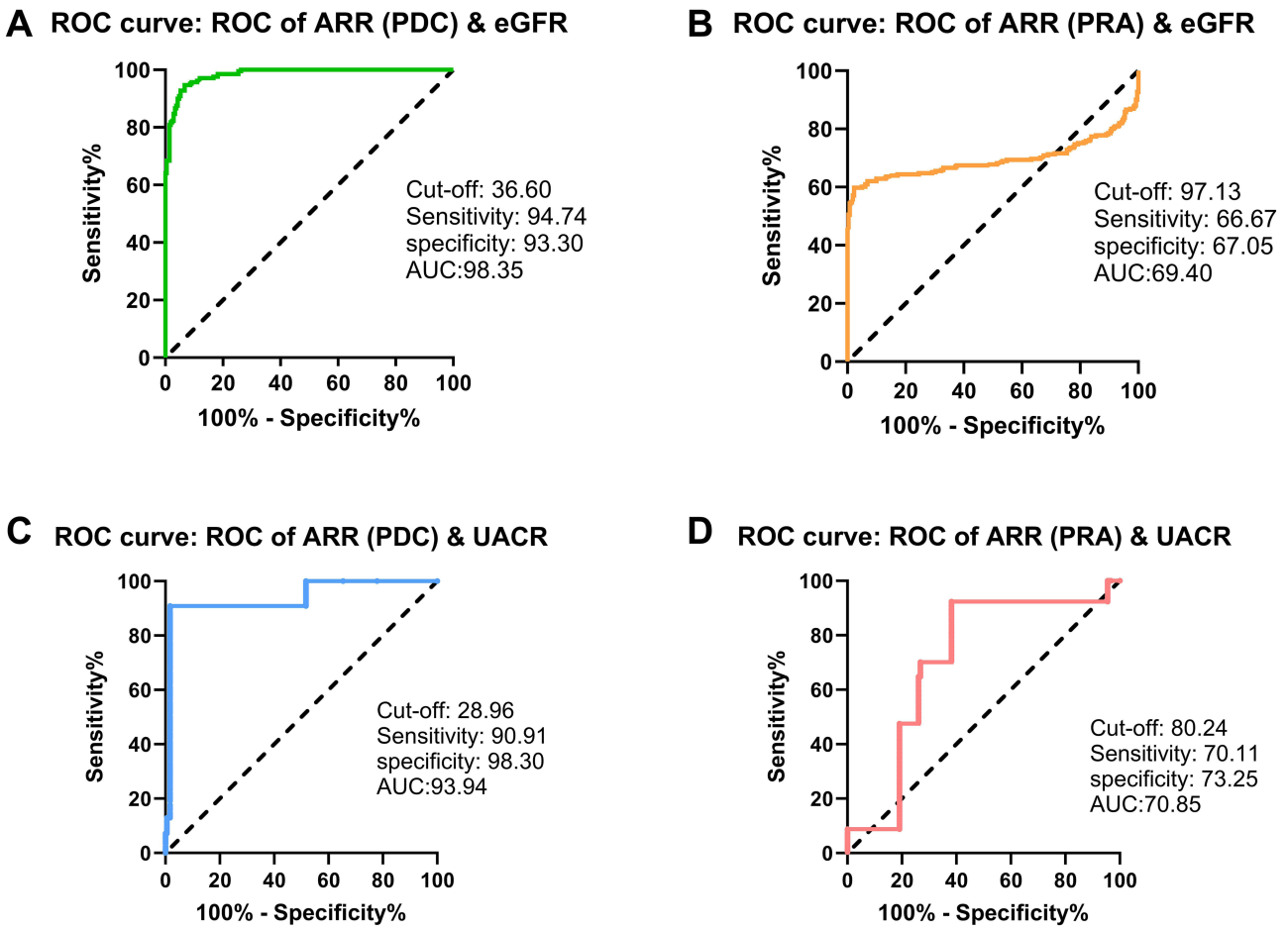

Figure 6 The predict value of ARR for the renal glomerular lesion via the PDC (**A**) and PRA (**B**) for eGFR, while UACR (**C** and **D**). The Cut-off, sensitivity, specificity, and AUC were annotated in the figure below the curve.

Abbreviations: ARR, aldosterone to renin ratio; ROC, receiver operating characteristic curve; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

a lower distribution in ARR quartile I (high renin levels) among drug-naïve individuals, where ARBs and diuretics were often used.

We examined how elevated ARR affects kidney function. We found lower levels of UACR and eGFR and higher levels of BUN and SCr in quartiles I and IV. However, we did not see a similar pattern in Cys, which is a sensitive marker of kidney injury that might be more affected by increased renin levels. Next, we looked at the effect of ARR on renal tubular injury markers. We found no consistent changes in the markers for renal tubular damage, such as NAG, suggesting that the tubular injury marker NAG may not be directly affected by changes in ARR.

Subsequently, we also did not find significant changes in other electrolytes, despite the increased sodium level due to the increased production of Ald. Interestingly, we observed a similar change in serum iron levels as seen with renal glomerular function, indicating that an imbalanced ARR may affect the regulation of serum iron.[43] We observed a declining trend in calcium levels, suggesting that higher ARR may increase eGFR lesions, resulting in calcium loss and changes in PTH levels, which were consistent with the trend shown in the multilinear regression model we presented later.

More stepwise correlational explorations consistently revealed that the ARR change could be significantly related to gender, SBP, and renal glomerular function in both the PDC and PRA assays. The results suggested that elevation of ARR in T2DM could be closely associated with renal glomerular pathological changes.[44,45] The findings also showed that females may experience higher ARR and renin levels, aligning with previous studies.[46–49] We conducted comprehensive regression analyses on the independent parameters associated with ARR change. Besides renin and Ald, which

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had R square values of 0.465 and 0.607 respectively, we identified other influencing factors: magnesium, hypertension severity, thyroid hormone, PTH, 25-OH-Vit D, and hypertensive drug use in PDC, while FPG, uric acid, phosphorus, PTH, and γ-GGT were associated in PRA. This variation may be due to differences in PDC and PRA assays, as the regression models fit a linear pattern (data not shown), consistent with previous research.[50] Nevertheless, the trends of renal glomerular function response to ARR change were consistent across both groups. Furthermore, ROC analysis indicated that ARR could serve as an alternative marker or candidate for evaluating renal glomerular function in DKD. Therefore, ARR could be used as an indicator for monitoring DKD progression.

Accumulated evidence has confirmed the roles of the sympathetic nervous system and RAAS in T2DM and metabolic diseases. These activations worsen metabolic syndrome by raising blood pressure and hormone levels and increasing the risk of pan-cardiovascular complications.[51,52] Aldosterone and renin are the most significant contributors to the sympathetic network, which lead to pathological changes in the kidney, including increased oxidative stress and inflammation, disruption of the infiltration barrier, fibrosis, and sclerosis of the glomerular membrane.[30,53,54] As a result, the ARR, which serves as an indicator for the levels of renin and Aldosterone, can reflect the severity of renal impairment in DKD. It has also been shown that medications targeting systemic RAAS effectively reduce impairment of the local microvascular system in T2DM, including retinopathy and nephropathy. These drugs include ACEI, ARB, and selective mineralocorticoid receptor antagonists like finerenone.[55–57] Previous research suggests that overstimulation of the sympathetic nervous system (SNS) and RAAS can be modified by sodium glucose co-transporter 2 inhibitors (SGLT-2i), which are jointly regulated by nuclei within the hypothalamus and brainstem associated with cardiovascular activity, such as the paraventricular nucleus of the hypothalamus (PVN) and the solitary tract nucleus (NTS).[58,59] This regulation could potentially influence the production of corticotropin-releasing hormone (CRH), anti-vasopressin (AVP), and the tone of pre-sympathetic nervous efferents relayed to the brainstem.[60,61] Therefore, future research is essential to clarify the relationship between the central SNS and ARR, as this may contribute to the pathogenesis of diabetic cardiovascular complications.

Limitations

We did not perform conversions for the PDC and PRA because there is insufficient evidence supporting their stability. However, we excluded cases with a history of PA outside our criteria, and the ARR values in this study did not exceed the cutoff established by our hospital for PA (PDC: 57 ng/mL/ng/mL, PRA: 300 ng/L/μg/L·h, after unit conversion, which aligns with the current diagnostic and treatment standards and guidelines).

Conclusion

This clinical study demonstrated the profile of aldosterone and renin in diabetic patients with DKD. The ARR values in the PDC and PRA groups were used to categorize the patients into four quartiles. A decline in renal glomerular filtration function was observed with higher renin concentrations and activity, as well as higher ARR. We found a well-established correlation between ARR and renal glomerular filtration function and developed models of effective predictors of ARR change using PDC and PRA measurements. ARR could serve as an alternative indicator for predicting the progression of DKD. The findings in the real world may support, in future analyses, the rationale for using selective mineralocorticoid receptor antagonists, such as finerenone, for the treatment of DKD.

Data Sharing Statement

De-identified data can be requested from the corresponding author.

Human Ethics and Consent to Participate Declarations

This retrospective study was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Shanghai Pudong Hospital (Approval No. 2025-IIT-013-E01). Since the study involved analyzing anonymized electronic medical records without direct patient interventions, the Ethics Committee waived the requirement for individual consent (NO.2025-IIT-013-E01). All patients had previously provided written informed consent during hospitalization to use their de-identified medical

data for research purposes, in line with institutional policies and ethical guidelines. To protect confidentiality, all personal identifiers (for example, names, ID numbers) were removed, and the anonymized data were securely stored on an encrypted server accessible only to authorized study personnel. The data will be kept for five years after the study's completion and then destroyed to preserve patient privacy. The study received no external funding.

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Author Contributions

Song Wen: Data Curation, Writing – original draft; **Zhinmin Xu**: Data curation, resources; **Min Gong**: Methodology, Resources; **Congcong Wang**: Data curation, Visualization, Resources; **Yue Yuan**: Investigation, Data curation, Resources; **Yanyan Li**: Methodology, Resources; **Meiyuan Dong**: Data curation, Resources; **Chaoxun Wang**: Methodology, Investigation, Resources **Dongxiang Xu**: Methodology, Investigation, Data Curation; **Xinlu Yuan**: Investigation, Resources; **Ligang Zhou**: Conceptualization, Funding acquisition, Validation, Writing – review & editing.

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there is no conflict of interest.

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