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ORIGINAL RESEARCH

Correlational Analysis of Resistant Hypertension with Diabetes Mellitus, Chronic Kidney Disease, and the Interplay of Sodium, Calcium, Magnesium, and Phosphorus

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Objective: To analyze the relationship between resistant hypertension (RH) and hypertension, diabetes mellitus, chronic kidney disease, sodium, calcium, magnesium, phosphorus.

Methods: A total of 475 patients with hypertension admitted to Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine from January 2021 to December 2023 were divided into hypertension group (HT group) and resistant hypertension group (RH group). We compared the differences between these two groups, and analyzed the influencing factors of RH, as well as the correlation between RH and the course of hypertension, diabetes mellitus, chronic kidney disease, and levels of sodium, calcium, magnesium and phosphorus.

Results: Compared with HT group, RH group had a significantly higher blood pressure ($P < 0.05$), longer duration of hypertension, diabetes mellitus, and chronic kidney disease ($P < 0.01$) and a higher proportion of combined chronic kidney disease ($P = 0.006$). The duration of hypertension, serum sodium ion concentration (≥142.00 mmol/L), calcium ion concentration (2.19 to < 2.30 mmol/L), and 24h urinary phosphorus ion level were independent influencing factors of RH ($P < 0.05$).

Conclusion: For hypertension patients with diabetes mellitus or chronic kidney disease, the risk of RH is significantly higher. The risk of RH may be lower in patients with blood sodium <142.00 mmol/L, blood calcium >2.29 mmol/L, 24h urine sodium and magnesium ions of 116.52 and 2.69 mmol, respectively, and higher 24h urine phosphorus ions.

Keywords: resistant hypertension, diabetes mellitus, chronic kidney disease, influence factor, correlation analysis

Introduction

Hypertension is a prevalent chronic disease that is closely associated with diabetes mellitus and chronic kidney disease (CKD). Hypertension and diabetes mellitus act as mutual risk factors, with the risk of diabetes mellitus in hypertensive patients being 2.5 times higher than that in individuals with normal blood pressure.[1] In China, the prevalence of hypertension among diabetic patients is as high as 54%.[2] The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a 10 mmHg reduction in systolic blood pressure is associated with a 12% decrease in the risk of diabetes mellitus-related complications, a 17% decrease in d diabetes mellitus-related mortality, and a 13% decrease in the risk of microvascular complications.[3] Additionally, hypertension is a significant risk factor for CKD. Compared with

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non-CKD individuals, the prevalence of hypertension in CKD patients is higher, reaching 67.3%.[4] In 2019, there were approximately 150 million CKD patients in China, accounting for 10.6% of the Chinese population.[5] Among hospitalized CKD patients, hypertensive nephropathy accounted for as high as 20.78%.[6] Therefore, hypertension is closely related to both diabetes and CKD.

Resistant hypertension (RH) represents a challenging aspect of hypertension management. The definition of RH varies slightly across different countries but generally includes blood pressure remaining above the target level despite treatment with ≥3 antihypertensive medications (including a diuretic or thiazide diuretic) or requiring four or more antihypertensive medications to control blood pressure.[7,8] In China, the definition of RH is stricter, emphasizing lifestyle modification and adequate antihypertensive medication treatment for at least 4 weeks.[9] The prevalence of RH among hypertensive patients is not low. A survey study involving 4158 hypertensive patients in the United States found that the proportion of RH was 19.7%.[10] Another meta-analysis including 91 studies and over 3.2 million hypertensive patients showed an RH prevalence of 10.3%, with the prevalence of RH among CKD patients as high as 22.9%.[11] In China, an observational study involving 1455 primary hypertensive patients from the southeastern region also found that the proportion of RH exceeded 12%.[12] With China's economic development and aging population, the number of hypertensive patients is expected to increase gradually, and the number of RH patients will also rise accordingly. However, research on the relationship between RH and the disease course of diabetes and CKD is currently limited.

Sodium, calcium, magnesium, and phosphorus are essential electrolytes that play critical roles in human physiology and can serve as surrogate markers of metabolic status. Their concentrations are readily measurable in clinical practice through routine blood and urine analyses. Both hypertension and related comorbidities, such as diabetes and CKD, are known to influence the homeostasis of these electrolytes. However, the potential relationships between the levels of these electrolytes in blood and urine and the pathogenesis of RH have been scarcely investigated. Therefore, this study aims to investigate the associations between RH and the disease course of hypertension, diabetes mellitus, and CKD, as well as the levels of sodium, calcium, magnesium, and phosphorus ions in blood and urine. We hypothesize that these factors may influence the pathophysiology of RH. By analyzing these variables, we intend to identify some key determinants of RH and provide valuable clinical insights for its prevention and management.

Subjects and Methods

Study Population

The study enrolled hypertension inpatients from Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, between January 2021 and December 2023. Inclusion was all patients who meet the diagnostic criteria for hypertension.[13] Exclusion criteria were: (1) pulmonary hypertension, secondary hypertension excluding renal hypertension, (2) diabetes mellitus types other than type 2, and (3) patients with incomplete clinical profiles. This research conformed to the tenets of the Declaration of Helsinki and received ethical approval from the aforementioned hospital's Ethics Committee (Approval No.: 2020LCSY044). Informed consent was obtained from all participants.

Methodological Approach

Diagnostic Criteria

Hypertension was diagnosed according to the 2018 Chinese guidelines for the management of hypertension[13]: SBP ≥140 mmHg and/or DBP ≥90 mmHg on three separate visits without antihypertensive medication, or a documented history of hypertension. The diagnosis of RH was made based on the aforementioned guidelines,[13] where blood pressure remained above the target levels despite the concurrent use of three antihypertensive agents at maximum tolerated doses, including a thiazide diuretic, for a minimum of four weeks, necessitating at least four agents to achieve target blood pressure. Type 2 diabetes mellitus was diagnosed per the Guideline for the prevention and treatment of type 2 diabetes mellitus in China (2020 edition):[14] characteristic symptoms of diabetes mellitus plus random plasma glucose ≥ 11.1 mmol/L, or fasting plasma glucose ≥ 7.0 mmol/L, or 2-hour plasma glucose ≥ 11.1 mmol/L following an oral glucose tolerance test (OGTT), or HbA1c ≥ 6.5%. Chronic kidney disease was diagnosed following the Guidelines for early screening, diagnosis, prevention and treatment of chronic kidney disease (2022 Edition):[15] evidence of kidney

damage (albuminuria, abnormal urinary sediment, renal tubular disorders, histological abnormalities, imaging abnormalities, or renal transplant) or a sustained decrease in glomerular filtration rate for over three months.

Data Collection

Comprehensive clinical data were systematically collected, encompassing demographic details and clinical parameters such as gender, age, hypertension duration, presence of diabetes mellitus, diabetes mellitus duration, presence of chronic kidney disease, chronic kidney disease duration, and antihypertensive medications usage. Antihypertensive medications include angiotensin receptor-neprilysin inhibitor (ARNI), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blocker (CCB), diuretics, beta-blockers, and alpha receptor blockers. Other antihypertensive medications are not within the scope of this study. The 24-hour average systolic and diastolic blood pressure were measured using the TM-2430 ambulatory blood pressure monitor. The cuff was secured on the patient's left upper arm, with the lower edge of the cuff positioned 2–3 cm above the elbow crease. The device was set to automatically inflate and measure the blood pressure every 20 minutes from 8:00 to 20:00 (daytime), and every 30 minutes from 20:00 to 8:00 the next day (nighttime).

Group Assignment

Individuals meeting the criteria for RH were classified into the resistant hypertension group (RH group), while those not fulfilling these criteria were allocated to the essential hypertension group (HT group).

Laboratory Assessments

Post an 8 to 12-hour overnight fast, venous blood samples were drawn at 07:00 for the quantification of serum sodium, calcium, and magnesium ion concentrations. Following the same fasting period, a 24-hour urine collection was initiated at 06:00 to evaluate the urinary excretion levels of sodium, calcium, magnesium, and phosphorus ions. Owing to the critical role of serum potassium in clinical management, clinicians frequently administer potassium supplements or potassium-lowering agents either prior to or on the day of hospital admission to normalize potassium levels. Consequently, fasting serum potassium levels measured the following morning may not reliably reflect the patient's true potassium status over the preceding period. Therefore, serum potassium levels were not included as an observation parameter in this study.

Statistical Analysis Methodology

Data were analyzed using SPSS version 20.0 and the R version 4.2.2 programming environment. Continuous variables adhering to a normal distribution were characterized by the mean ± standard deviation ($\bar{x} \pm s$), with group comparisons performed utilizing Student's *t*-test. Non-normally distributed continuous variables were depicted using the median and interquartile range [M(Q1, Q3)], with group comparisons conducted via the Mann–Whitney *U*-test. Categorical variables were presented as frequencies, with group comparisons made using the chi-square test. Univariate logistic regression analysis was employed to assess the association of age, gender, duration of hypertension, diabetes mellitus, diabetes mellitus duration, chronic kidney disease, chronic kidney disease duration, serum sodium, calcium, and magnesium ion concentrations, and 24h urinary excretion of sodium, calcium, magnesium, and phosphorus ions with RH. Diabetes mellitus and chronic kidney disease durations were stratified into two subgroups based on the median value, while other continuous variables were categorized into tertiles according to the upper and lower quartile. Variables exhibiting statistical significance in univariate analysis were subjected to multivariate logistic regression analysis. The correlation between RH and the aforementioned variables was further explored using Restricted Cubic Splines (RCS), with critical values determined for each association. Statistical significance was set at $P < 0.05$.

Results

Demographic and Clinical Characteristics

The study encompassed 475 hypertensive patients, including 257 males and 218 females, with 407 individuals in the HT group and 68 in the RH group. The mean age was 64.83 ± 14.00 years, and the median duration of hypertension was

12.00 (IQR: 4.00 to 21.00) years. Of these, 239 patients had comorbid diabetes mellitus with a median duration of 0.00 (IQR: 0.00 to 10.50) years, and 207 had comorbid CKD with a median duration of 0.00 (IQR: 0.00 to 5.00) years.

Compared with the HT group, the RH group exhibited significantly higher 24-hour average systolic and diastolic blood pressures ($P < 0.001$, $P = 0.043$) and higher usage rates of antihypertensive medications, including ARNI, CCB, diuretics, beta-blockers, and alpha receptor blockers ($P < 0.001$). However, no significant differences were observed in the use of ACEI/ARB between the two groups ($P > 0.05$). Compared with the HT group, the RH group had longer disease durations of hypertension, diabetes mellitus, and chronic kidney disease ($P < 0.01$), a higher proportion of patients with CKD ($P = 0.006$), lower serum calcium ion concentrations ($P = 0.020$), and lower 24-hour urinary calcium and phosphate ion levels ($P < 0.01$). No significant differences were found in the remaining parameters between the two groups ($P > 0.05$). For detailed comparisons, refer to Table 1.

Analysis of Factors Influencing Resistant Hypertension

In an initial univariate logistic regression analysis, we evaluated the potential association of various factors with RH, including age, gender, duration of hypertension, presence of diabetes mellitus, diabetes mellitus duration, CKD, CKD duration, serum sodium, calcium, and magnesium ion concentrations, and 24h urinary excretion levels of sodium, calcium, magnesium, and phosphorus ions. It was observed that the duration of hypertension, CKD status, CKD duration, serum sodium ion concentration at or above 142.00 mmol/L, serum calcium ion concentration, 24h urinary calcium ion levels at or above 3.90 mmol, and urinary phosphorus ion levels were significantly associated with RH ($P < 0.05$). Other factors did not yield statistically significant results ($P > 0.05$).

Table 1 Basic Clinical Data of Hypertension Patients[$\bar{x} \pm s$/M (Q_1~Q_3)]

	Total (*n*=475)	HT group (*n*=407)	RH group (*n*=68)	χ^2/*t*/*Z*	*P*
Male/female, n	257/218	220/187	37/31	<0.01	0.956
Age, years	64.83 ± 14.00	64.51 ± 14.15	66.78 ± 12.99	−1.24	0.216
Hypertension duration, years	12.00 (4.00~21.00)	12.00 (3.00~20.00)	17.00 (8.75~22.25)	−2.66	0.008*
Diabetes mellitus, n(%)	239 (50.32)	198 (48.65)	41 (60.29)	3.16	0.075
Diabetes mellitus duration, years	0.00 (0.00~10.50)	0.00 (0.00~10.00)	5.00 (0.00~15.00)	−2.37	0.018*
Chronic kidney disease, n(%)	207 (43.58)	167 (41.03)	40 (58.82)	7.50	0.006*
Chronic kidney disease duration, years	0.00 (0.00~5.00)	0.00 (0.00~5.00)	3.00 (0.00~7.00)	−2.69	0.007*
Antihypertensive medications, n(%)					
ARNI	70 (14.7%)	43 (10.6%)	27 (39.7%)	39.38	<0.001*
ACEI/ARB	165 (34.7%)	144 (35.4%)	21 (30.9%)	0.52	0.471
CCB	300 (63.2%)	244 (60.0%)	56 (82.4%)	12.57	<0.001*
Diuretics	65 (13.7%)	24 (5.9%)	41 (60.3%)	145.97	<0.001*
Beta-blockers	187 (39.4%)	138 (33.9%)	49 (72.1%)	35.53	<0.001*
Alpha receptor blockers	75 (15.8%)	42 (10.3%)	33 (48.5%)	63.98	<0.001*
24-hour average SBP, mmHg	142 ± 18	140 ± 18	151 ± 20	−4.25	<0.001*
24-hour average DBP, mmHg	81 ± 11	80 ± 11	83 ± 11	−2.05	0.043*
Serum concentration					
Sodium ion, mmol/L	140.72 ± 2.83	140.62 ± 2.85	141.27 ± 2.64	−1.76	0.080
Calcium ion, mmol/L	2.23 ± 0.19	2.24 ± 0.19	2.18 ± 0.18	2.34	0.020*
Magnesium ion, mmol/L	0.87 ± 0.13	0.87 ± 0.13	0.88 ± 0.12	−0.51	0.607
24-hour urinary level					
Sodium ion, mmol	137.80 (104.50~179.30)	137.80 (106.20~178.10)	138.60 (78.10~185.45)	−0.76	0.446
Calcium ion, mmol	2.61 (1.05~4.90)	2.79 (1.08~5.14)	1.60 (0.63~3.44)	−3.07	0.002*
Magnesium ion, mmol	3.05 (2.10~4.13)	3.08 (2.22~4.13)	2.85 (1.42~4.16)	−1.92	0.055
Phosphorus ion, mmol	15.46 (11.03~19.65)	15.62 (11.34~20.50)	12.12 (6.40~17.80)	−3.65	<0.001*

Note: *P<0.05.

Abbreviations: ARNI, angiotensin receptor-neprilysin inhibitor; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure.

A subsequent multivariate logistic regression analysis was conducted on the factors that demonstrated statistical significance in the univariate analysis. This analysis identified the duration of hypertension, serum sodium ion concentration at or above 142.00 mmol/L, serum calcium ion concentration within the range of 2.19 to less than 2.30 mmol/L, and 24h urinary phosphorus ion levels as independent determinants of RH ($P < 0.05$). For comprehensive insights, please refer to Table 2.

Table 2 Results of Logistic Regression Analysis (n=475)

	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age, years						
< 61	—	—				
61~< 71	1.79	0.91~3.51	0.089			
≥ 71	1.66	0.86~3.22	0.131			
Sex						
Female	—	—				
Male	1.01	0.61~1.70	0.956			
Hypertension duration, years						
< 7	—	—		—	—	
7~< 20	2.37	1.11~5.02	0.025*	2.47	1.09~5.60	0.030*
≥ 20	3.23	1.57~6.65	0.001*	3.19	1.45~7.01	0.004*
Diabetes mellitus						
No	—	—				
Yes	1.60	0.95~2.70	0.077			
Diabetes mellitus duration, years						
< 7	—	—				
≥ 7	1.68	1.00~2.84	0.051			
Chronic kidney disease						
No	—	—		—	—	
Yes	2.05	1.22~3.46	0.007*	0.56	0.12~2.67	0.469
Chronic kidney disease duration, (years)						
< 3	—	—		—	—	
≥3	2.50	1.48~4.23	<0.001*	3.45	0.75,15.96	0.113
Serum concentration						
Sodium ion, mmol/L						
< 140.00	—	—		—	—	
140.00~< 142.00	1.03	0.51~2.07	0.929	1.02	0.49~2.14	0.959
≥142.00	2.00	1.06~3.79	0.033*	2.01	1.02~3.97	0.043*
Calcium ion, mmol/L						
< 2.19	—	—		—	—	
2.19~< 2.30	0.45	0.24~0.85	0.013*	0.49	0.24~0.98	0.044*
≥2.30	0.48	0.26~0.89	0.021*	0.60	0.29~1.23	0.164
Magnesium ion, mmol/L						
< 0.83	—	—				
0.83~< 0.90	1.43	0.70~2.90	0.325			
≥0.90	1.65	0.83~3.30	0.156			
24-hour urinary level						
Sodium ion, mmol/L						
< 113.00	—	—				
113.00~< 162.00	0.55	0.28~1.08	0.083			
≥162.00	0.98	0.54~1.77	0.939			

(*Continued*)

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Table 2 (Continued).

	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	**95% CI**	***P***	**OR**	**95% CI**	***P***
Calcium ion, mmol						
< 1.39	—	—		—	—	
1.39~< 3.90	0.73	0.41~1.32	0.299	1.16	0.59~2.25	0.670
≥3.90	0.36	0.18~0.73	0.004*	0.92	0.37~2.27	0.859
Magnesium ion, mmol						
< 2.43	—	—				
2.43~< 3.73	0.56	0.30~1.05	0.072			
≥3.73	0.66	0.36~1.22	0.184			
Phosphorus ion, mmol						
< 12.40	—	—		—	—	
12.40~< 18.30	0.48	0.26~0.88	0.018*	0.45	0.23~0.86	0.017*
≥18.30	0.34	0.17~0.66	0.001*	0.34	0.16~0.72	0.005*

Note: *P<0.05.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Correlative Analysis of Resistant Hypertension With the Duration of Underlying Diseases

A Restricted Cubic Spline correlation analysis was performed to delineate the association between RH and the chronicity of hypertension, diabetes mellitus, and chronic kidney disease. The findings revealed significant correlations between RH and the disease durations for hypertension, diabetes mellitus, and chronic kidney disease (P=0.037, Figure 1A; P=0.024, Figure 1B; and P=0.006, Figure 1C, respectively).

Although the linearity of the association between RH and the durations of hypertension and diabetes mellitus was approached but not achieved statistical significance (P-Nonlinear=0.060 and P-Nonlinear=0.063, respectively), the trend analysis suggested the existence of maximum inflection points at 22.86 (Figure 1A) and 13.72 (Figure 1B) years, respectively. In contrast, a significant curvilinear relationship was observed between RH and the duration of chronic kidney disease (P-Nonlinear=0.007), with the maximum inflection point identified at 5.50 years (Figure 1C). These data suggest that the risk of RH is maximized at disease durations of 22.86 years for hypertension, 13.72 years for diabetes mellitus, and 5.50 years for chronic kidney disease. For graphical representation of these trends, see Figure 1.

Correlative Analysis of Resistant Hypertension With Some Ion Concentrations

A Restricted Cubic Spline correlation analysis was also undertaken to investigate the relationship between RH and the concentrations of serum sodium, calcium, and magnesium ions, as well as the 24h urinary excretion levels of sodium, calcium, magnesium, and phosphorus ions. The results indicated significant correlations between RH and serum calcium ion concentration, and the 24h urinary levels of sodium, calcium, magnesium, and phosphorus ions (P=0.043, Figure 2A; P=0.001, Figure 2B; P=0.033, Figure 2C; P<0.001, Figure 2D; and P<0.001, Figure 2E, respectively), with no significant associations observed for other variables (P>0.05).

The correlation between RH and serum calcium ion concentration appeared to be linear (P-Nonlinear=0.197), with the maximum slope for RH occurring at a serum calcium concentration of 2.29 mmol/L (Figure 2A). RH demonstrated significant curvilinear correlations with the 24h urinary levels of sodium and magnesium ions (P-Nonlinear<0.001 and P-Nonlinear=0.003, respectively), with the nadir inflection points occurring at 116.52 mmol for sodium (Figure 2B) and 2.69 mmol for magnesium (Figure 2C). The relationships between RH and the 24h urinary levels of calcium and phosphorus ions were linear (P-Nonlinear=0.918, Figure 2D and P-Nonlinear=0.067, Figure 2E, respectively).

These data suggest that the probability of RH diminishes sharply at serum calcium concentrations exceeding 2.29 mmol/L. The lowest likelihood of RH is indicated at 24h urinary sodium and magnesium levels of 116.52 mmol

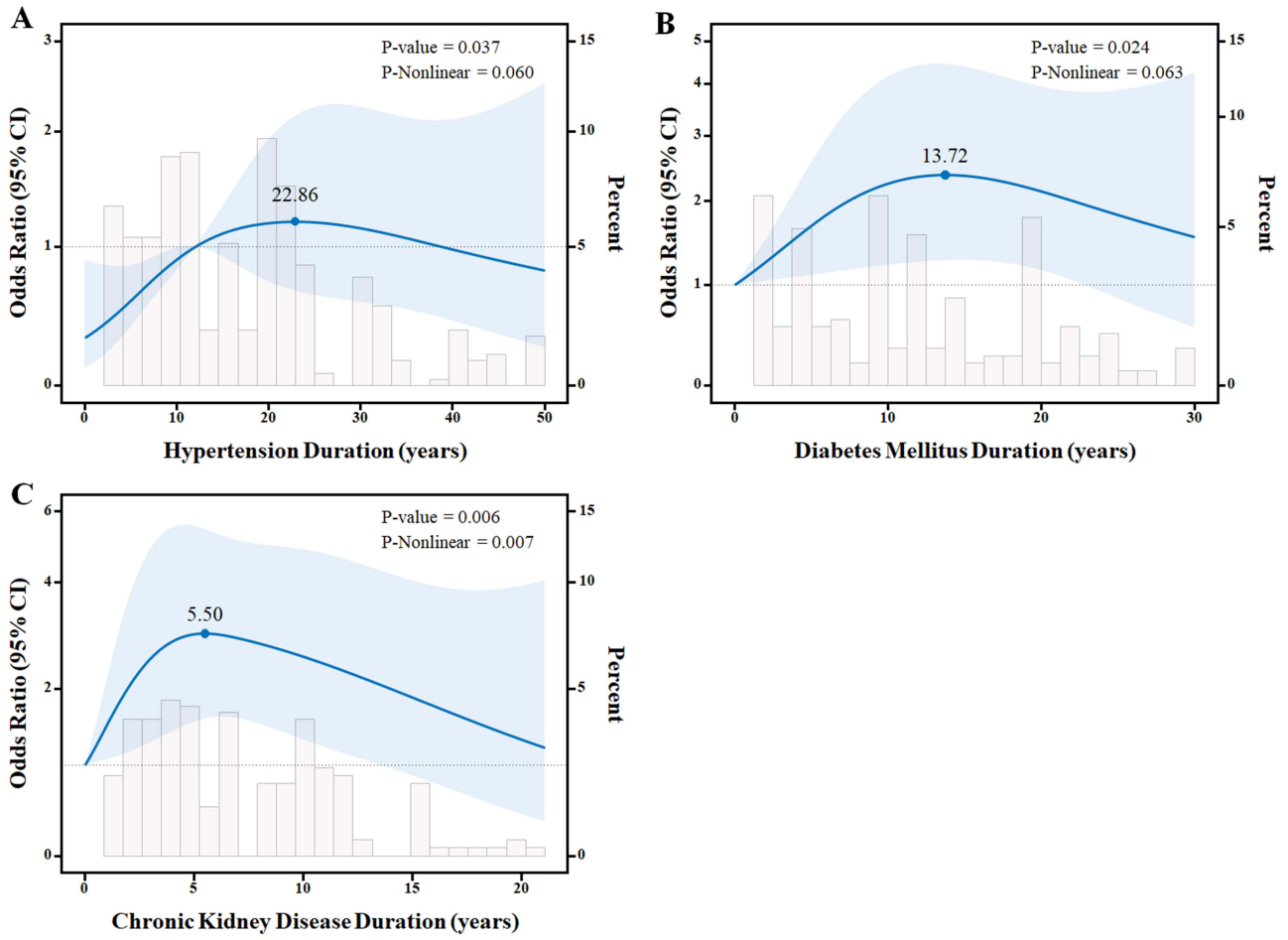

Figure 1 Correlation between RH and disease course. (**A**) hypertension duration (years), dot: the maximum inflection point, (**B**) diabetes mellitus duration (years), dot: the maximum inflection point, (**C**) chronic kidney disease duration (years), dot: the maximum inflection point.
Abbreviations: RH, resistant hypertension; CI, confidence interval.

and 2.69 mmol, respectively. Additionally, elevated serum calcium and 24h urinary calcium and phosphorus ion levels are inversely associated with the likelihood of RH. For graphical depiction of these relationships, refer to Figure 2.

Discussion

Hypertension is a vital risk factor for both cardiovascular and renal disease progression. In particular, resistant hypertension (RH) is intricately linked to chronic kidney disease (CKD).[16] The kidneys are crucial to blood pressure regulation, and their dysfunction can precipitate a cascade of pathophysiological events. Impaired renal excretion of sodium and water leads to increased blood volume, while overactivation of the renin-angiotensin-aldosterone system (RAAS) drives glomerulosclerosis and renal interstitial fibrosis. Declining renal function may also induce secondary hyperparathyroidism and calcium-phosphate metabolic disturbances, culminating in ectopic deposition of calcium phosphate salts in the vascular wall and subsequent vascular calcification.[17] Additionally, the accumulation of metabolic waste products can damage endothelial cells, exacerbating vascular injury.[18] Collectively, these mechanisms contribute to elevated blood pressure and the development of RH. Clinical studies have underscored the prevalence and impact of RH in CKD populations. A German observational study of 4901 CKD patients reported a 38% prevalence of RH, with RH patients exhibiting higher rates of major cardiovascular events and CKD progression.[19] Similarly, a US survey of over 68,000 CKD patients revealed RH prevalence ranging from 23% to 31%, with a clear correlation between higher CKD stages and increased RH prevalence.[20] Another cohort study involving 3367 hypertensive CKD patients demonstrated a 40.4% RH prevalence, accompanied by significantly elevated risks of myocardial infarction, heart failure, and all-cause

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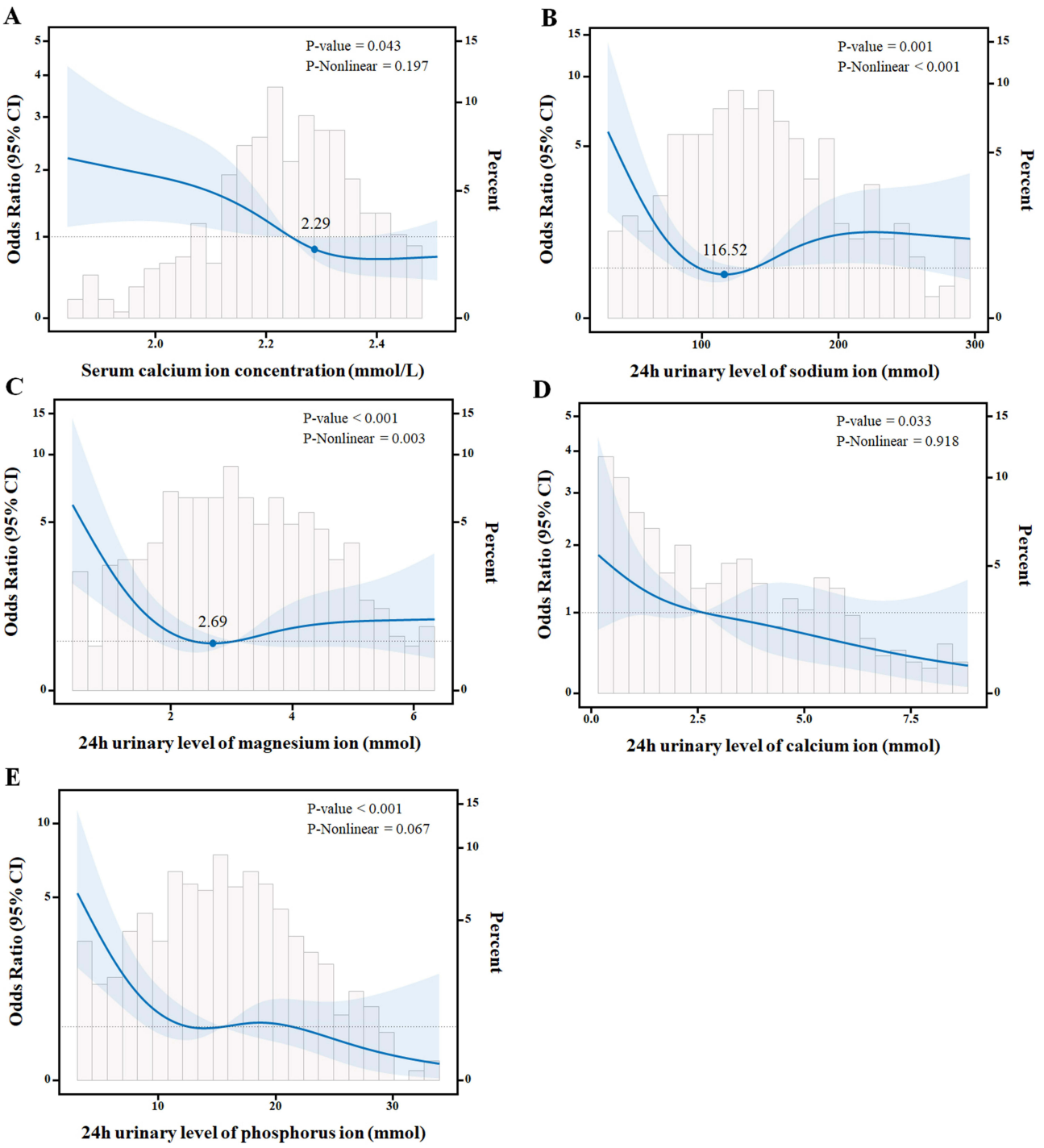

Figure 2 Correlation between RH and various ions in serum and 24h urine. (**A**) serum calcium ion concentration (mmol/L), dot: the maximum slope, (**B**) 24h urinary level of sodium ion (mmol), dot: the nadir inflection point, (**C**) 24h urinary level of magnesium ion (mmol), dot: the nadir inflection point, (**D**) 24h urinary level of calcium ion (mmol), and (**E**) 24h urinary level of phosphorus ion (mmol).
Abbreviations: RH, resistant hypertension; CI, confidence interval.

mortality compared to non-RH patients.[21] In our study, we observed that CKD prevalence and duration were significantly higher in the RH group compared to the HT group. Univariate logistic regression analysis revealed significant associations, and restricted cubic spline (RCS) analysis identified a CKD duration of 5.5 years as the point of maximal RH likelihood. These findings align with previous research indicating that CKD patients often develop drug resistance, particularly to antihypertensive medications, resulting in suboptimal efficacy despite combination therapy.[22] Consistent

with this, our study showed higher proportions of antihypertensive drug use and elevated blood pressure levels in the RH group compared to the HT group. These results corroborate those of prior investigations and highlight the complex interplay between CKD and RH.

RH is also closely linked to diabetes mellitus, with insulin resistance being a key shared pathophysiological mechanism underlying both conditions.[23] Insulin resistance activates vascular NADPH oxidase, leading to excessive production of reactive oxygen species (ROS). This, in turn, induces vascular inflammation, endothelial dysfunction, and vasoconstriction.[24] Concurrently, hyperinsulinemia can overstimulate the RAAS and the sympathetic nervous system, promoting sodium and water retention and accelerating vascular stiffness.[25] Collectively, these mechanisms exacerbate hypertension and heighten the risk of RH. In our study, although the prevalence of diabetes mellitus did not differ significantly between groups, the duration of diabetes was markedly longer in the RH group compared to the HT group. While diabetes mellitus per se and its duration were not identified as independent risk factors for RH, RCS analysis revealed a significant association between RH and diabetes mellitus duration, with the highest likelihood of RH occurring at a diabetes mellitus duration of 13.72 years. In contrast, the highest likelihood of RH in relation to hypertension duration was observed at 22.86 years. These findings suggest that in patients with isolated hypertension, progression to RH may take approximately 20 years. However, in patients with comorbid diabetes mellitus, RH may develop within 13 years, and in those with CKD, RH may emerge within approximately 5 years. Thus, both diabetes mellitus and CKD profoundly accelerate the transition from hypertension to RH, underscoring their synergistic impact on disease progression.

Pulmonary hypertension (PH) is highly prevalent among patients with CKD and is independently associated with adverse clinical outcomes.[26] However, the clinical classification of PH-CKD and the underlying pathophysiological mechanisms remain poorly understood.[27] Given the complexity and heterogeneity of the pathophysiology and clinical features of PH-CKD, further characterization is needed to improve clinical management and patient outcomes. Therefore, PH was not included in the scope of this study.

In the elucidation of the relationships between ionic levels of sodium, calcium, magnesium, and phosphorus with RH, our investigation has revealed significant correlations. Notably, our study identified hypernatremia as an independent risk factor for RH, with the lowest likelihood of RH occurring at a 24h urinary sodium excretion rate of 116.52 mmol. It has been previously documented that RH patients exhibit an augmented sodium ion reservoir, and in patients with concurrent hypertension and chronic kidney disease, there is a compromised capacity for salt and water excretion, resulting in elevated serum sodium and diminished urinary sodium.[28] This renal sodium excretion deficit contributes to impaired sodium ion transport in hypertensive patients,[29] and the associated hypernatremia and fluid retention may impair the sodium-potassium pump, leading to a disruption of sodium-calcium exchange and an eventual buildup of intracellular calcium ions.[30] The consequent rise in intracellular calcium ion concentration augments the tone of arteriolar smooth muscle, thereby increasing peripheral vascular resistance, a key etiological factor in the hemodynamic perturbations observed in primary hypertensive patients.[31] These findings are congruent with our study's outcomes. However, the lack of a linear negative correlation between urinary sodium excretion and RH in our study may be attributed to the high prevalence of chronic kidney disease in our sample, which is characterized by sodium excretion impairments, necessitating further investigation.

An unexpected finding of our study was the inverse relationship between blood calcium ion concentration and RH, with higher calcium levels in the blood and greater urinary calcium excretion correlating with a reduced likelihood of RH. The mechanism behind this association remains elusive and requires elucidation. It is hypothesized that the distinct roles of intracellular versus extracellular calcium ions, specifically the blood calcium ions, may be at play, but this warrants additional research and validation.

In the exploration of magnesium ion dynamics, we identified an intriguing threshold: the 24h urinary excretion of magnesium ions at 2.69 mmol marks the nadir for the likelihood of RH. Magnesium ions, integral as co-factors in enzymes that participate in the vascular signal transduction pathways, exert a dampening effect on the vasoconstriction triggered by heightened intracellular calcium ion concentrations.[32] A comprehensive meta-analysis, incorporating data from 34 double-blind, randomized, placebo-controlled trials involving 2028 participants, has corroborated the efficacy of oral magnesium supplementation in reducing blood pressure.[33] Parallel to our findings, a study with 5511 participants has delineated an inverse relationship between urinary magnesium excretion and the risk of hypertension.[34]

Our inquiry into the role of phosphorus ions has unveiled them as an independent determinant of RH, with urinary phosphorus levels demonstrating a robust negative linear correlation with RH susceptibility. Phosphorus ions are pivotal in the modulation of blood pressure through their multifaceted roles in plasma membrane structure, energy metabolism, enzymatic activation, cellular signaling, and acid-base balance, thereby profoundly influencing cellular integrity and function.[35] Notably, a cross-sectional examination suggests a link between elevated dietary phosphorus intake and reduced blood pressure.[36] Our study's constraints precluded the inclusion of serum phosphorus data; however, our focus on urinary phosphorus levels lays a foundation for future research to expand upon and delve deeper into these relationships.

Conclusions

Synthesizing these findings, we discern that the interplay between hypertension and comorbidities such as diabetes mellitus and chronic kidney disease escalates the risk of progression to RH, with the latter being a particularly influential factor. The confluence of low blood sodium, high blood calcium, and elevated 24h urinary phosphorus appears to mitigate the risk of RH. Nonetheless, the intricate mechanisms by which magnesium and phosphorus ions influence RH remain to be fully elucidated, underscoring the necessity for further research to demystify their roles.

Data Sharing Statement

The data and information supporting this study are available from the corresponding author, Yi-Hong Wei, upon reasonable request.

Ethics Approval and Consent to Participate

The treatment protocol and design of this study were approved by the Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine and were in accord with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all patients at the time of study enrollment.

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Disclosure

The authors declare that they have no competing interests.

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