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ORIGINAL RESEARCH

Plasma Aldosterone Elevation in Hypertensive Patients and Association with Urinary Stone Formation: A Large-Scale Population Study from Northwest China

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Background: Previous studies have suggested a potential association between plasma aldosterone concentration (PAC) and calcium regulation. However, it remains unclear whether elevated PAC levels increase the risk of urinary stones. Therefore, this study aimed to investigate the relationship between PAC levels and urinary stones, including their subtypes, in patients with hypertension.

Methods: This large-scale study included a total of 35161 hypertensive patients. Multivariable logistic regression was used to analyze the association between PAC levels and urinary stones, as well as their subtypes. Additionally, a dose-response relationship was explored using restricted cubic spline (RCS) analysis, and a two-stage comparative analysis was conducted based on the RCS turning point. The importance of PAC was further confirmed through variable importance analysis. Finally, extensive subgroup analyses and sensitivity analyses were performed to assess the robustness of the findings.

Results: Multivariable logistic regression revealed a significant association between elevated PAC levels and the occurrence of urinary stones and their subtypes. Specifically, for every 5 ng/dL increase in PAC, the risk of urinary stones increased by 26% (odds ratios [OR] 1.26, 95% confidence interval [CI], 1.22–1.30, P<0.001). Furthermore, RCS threshold analysis demonstrated a marked increase in urinary stone risk when PAC levels exceeded 14.2 ng/dL (OR 1.50, 95% CI, 1.38–1.63, P<0.001). These findings were consistent across subtypes, including kidney stones and ureteral stones. Subgroup analyses showed that the results were unaffected by stratification factors, and sensitivity analyses further confirmed the stability of the findings.

Conclusion: This study demonstrated that elevated PAC levels are significantly associated with the occurrence of urinary stones and their subtypes in hypertensive patients. These findings suggest that controlling PAC levels in hypertensive patients may help reduce the risk of urinary stone formation.

Keywords: Plasma aldosterone concentration, primary aldosteronism, Hypertension, Parathyroid hormone

Introduction

Urinary stones are a common urological condition characterized by the presence of stones in the renal pelvis, ureter, bladder, or urethra.[1] Among these, kidney stones (KS) and ureteral stones (US) are the most prevalent and clinically significant due to their potential to cause severe complications.[2] These stones can lead to impaired kidney function, chronic kidney disease, and a substantial economic burden associated with medical treatments and hospitalizations.[3,4]

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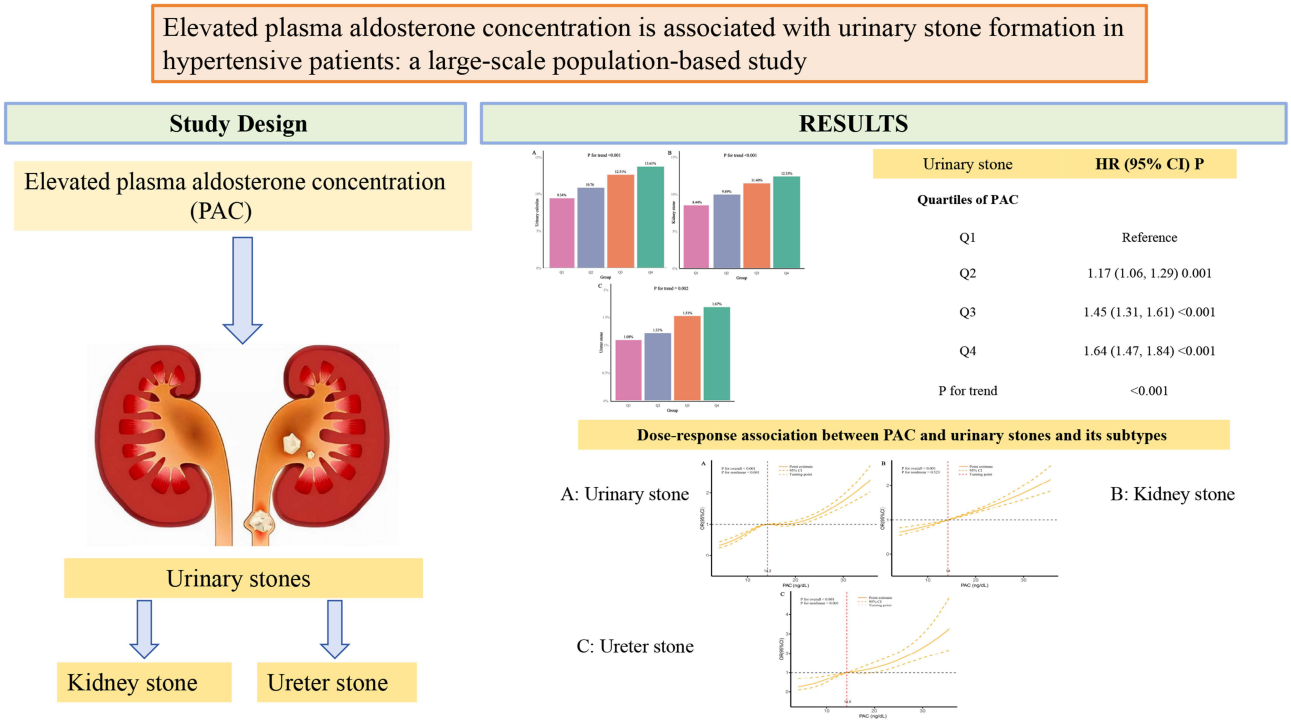
Graphical Abstract



Consequently, identifying risk factors for kidney and ureteral stones and developing effective prevention strategies have become critical priorities in the medical community.[5] Furthermore, with ongoing changes in dietary habits and environmental factors, the global incidence of urolithiasis is projected to increase, underscoring the urgency of addressing this public health issue.[6,7] Therefore, it is crucial to raise awareness about the dangers of urinary stones and the importance of proactive measures to prevent their formation.

Traditionally, the formation of urinary stones has been primarily attributed to dietary and environmental factors, such as excessive salt intake, low fluid consumption, and genetic predisposition.[8–12] The most common types of urinary stones include calcium oxalate (accounting for the majority of cases), followed by calcium phosphate, uric acid, struvite, and cystine stones.[13,14] Excessive dietary salt and protein intake are recognized as key contributors to hypercalciuria, a critical determinant of calcium-dependent KS formation.[12,15] Previously, high urinary calcium levels were attributed to the excessive absorption of intestinal calcium, leading to increased urinary calcium excretion.[16–19] However, the potential role of aldosterone—a hormone crucial for regulating water-salt balance and ion metabolism—has been largely overlooked in stone pathogenesis.

KS and US, as clinically important types of urinary calculi, are strongly associated with hypercalciuria. Emerging evidence indicates that elevated plasma aldosterone concentrations (PAC) significantly promote urinary calcium excretion - a well-established risk factor for urinary stone formation.[20–22] Animal studies have further corroborated this relationship, showing that aldosterone oversecretion not only increases urinary calcium excretion but also contributes to bone mass loss.[23,24] Supporting these findings, a clinical study in Taiwan revealed that patients with primary aldosteronism (PA) exhibit a significantly higher risk of developing KS.[25] These collective findings strongly suggest aldosterone's crucial role in urinary stone pathogenesis. Notably, aldosterone serves as an important diagnostic marker for secondary hypertension and refractory hypertension PA, implying its potential involvement in hypertensive-associated stone formation. Furthermore, hypertension - one of the world's most prevalent chronic conditions - frequently coexists with various metabolic abnormalities, creating additional pathways for urinary stone development. Despite these established

connections, the relationship between aldosterone and Urinary stones remains underexplored in the general hypertensive population. Given aldosterone's diagnostic significance in primary aldosteronism and the high global prevalence of both hypertension and urolithiasis, investigating stone etiology in hypertensive patients carries substantial clinical and public health importance.

Therefore, this study aims to explore the relationship between PAC and urinary stones and their subtypes in hypertensive patients, and reveal the potential association between the two, which may provide evidence for the prevention and treatment of urinary calculus in hypertensive patients in the future.

Material and Methods

Screening of the Study Population

Inclusion Criteria

These large-scale cross-sectional studies included patients with hypertension who visited the Xinjiang Hypertension Center between 2014 and 2024. A total of 42973 participants initially met our requirements.

Exclusion Criteria

Initially, we excluded participants who were missing urinary ultrasound or CT scans, leaving a total of 40624 participants who met the preliminary study criteria. Subsequently, we excluded individuals lacking PAC data, those with primary hyperparathyroidism, severe renal impairment, long-term use of salocorticoid receptor antagonists, and missing basic information [including serum calcium, 24-hour urinary calcium, and parathyroid hormone (PTH)]. After these screenings, 35161 participants were eligible for inclusion in the study. The selection process of the study population is illustrated in Figure 1.

The study was approved by the Ethics Committee of the People's Hospital of Xinjiang Uygur Autonomous Region (KY2022080904), following the guidelines of the Helsinki Declaration. Informed consent was obtained from all participants, and they signed consent forms before enrollments.

Data Collection and Definitions

Participants' general information, physical examination results, medical history, drug usage, and laboratory test data were collected from hospital electronic medical records and Medicare systems. The specific names and types of drugs used are listed in Table S1. Basic participant information, including height, weight, blood pressure, and body mass index (BMI),

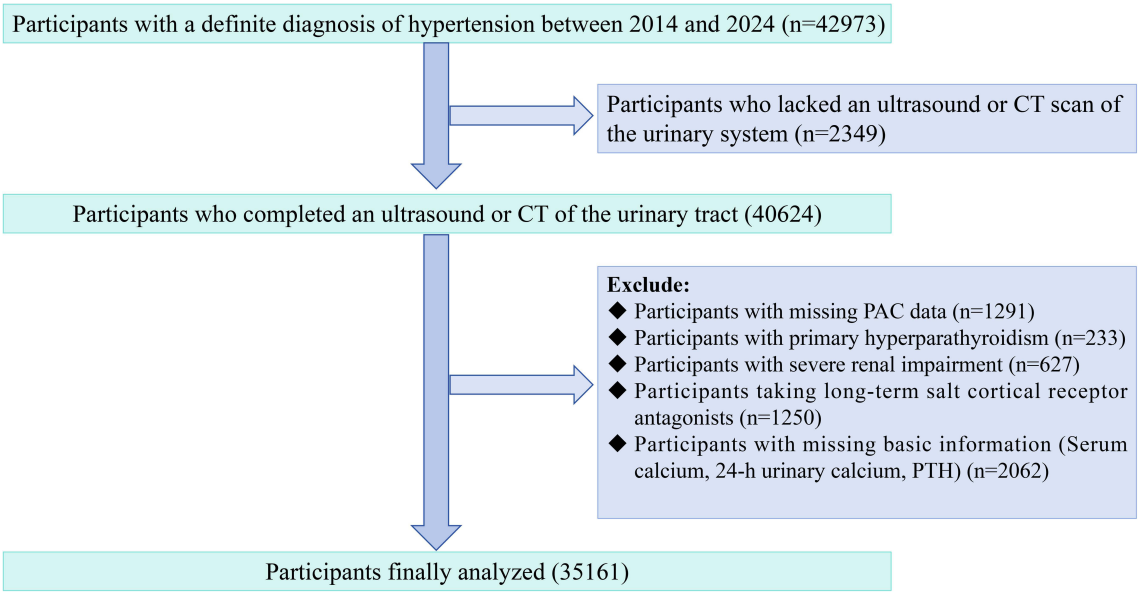


Figure 1 Flowchart for selection of study populations.

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was measured and calculated as detailed in the Supplementary Material. Data on various laboratory tests—such as creatinine, blood urea nitrogen, PTH, serum potassium, serum calcium, serum phosphorus, 24-hour urinary potassium, 24-hour urinary calcium, 24-hour urinary phosphorus, fasting plasma glucose; and thyroid stimulating hormone (TSH)—were measured using an automatic biochemical analyzer (Roche Diagnostics, Basel, Switzerland, c502). PAC was measured by radioimmunoassay (DSL-8600 ACTIVE Aldosterone Coated Tube Radioimmunoassay Kit; Diagnostic Systems Laboratories, Webster, TX), and plasma renin activity (PRA) was also measured by radioimmunoassay using a commercial kit (Northern China). Hormone measurements followed current guidelines and were consistent with those used in previous studies at the center.[26–29] Detailed information on the measurement methods can be found in the Supplementary Material. The definitions of various diseases, including coronary heart disease (CHD), diabetes mellitus (DM), dyslipidemia, PA, and cancer, are based on current diagnostic criteria. These criteria are further detailed in the Supplementary Material.

Study Outcomes

The primary outcome of this study was the presence of urinary stones, including its subtypes: KS and US. The diagnosis of urinary stones was primarily based on ultrasound or CT scan of the urinary system.

Statistical Analysis

We first divided participants into four groups based on quartiles of PAC levels for between-group comparisons. Multicollinearity was assessed using the variance inflation factor (VIF) and the results of the VIF showed no multicollinearity (Table S2). Multifactorial logistic regression with multiple models (five models were built) was then used to assess the association between PAC and urinary stones, as well as its subtypes, KS and US. Restricted cubic spline (RCS) was used to further assess the dose-response relationship between the two groups and a two-stage comparative analysis was performed based on the turning point. Additionally, Boruta feature importance analysis based on a logistic regression model of random forest was conducted to analyze the significant effect of PAC on urinary stones. Finally, extensive subgroup and sensitivity analyses were performed to confirm the robustness of the results. Detailed descriptions of the statistical analyses are provided in the Supplementary Material.

All statistical analyses were performed using version R.4.2.2, and a two-sided P-value of less than 0.05 was considered statistically significant.

Results

Characteristics of the Study Population

A total of 35161 hypertensive patients were included in this study, and Table 1 shows the basic characteristics of the participants, grouped according to PAC quartiles. Among these participants, 57.11% were male. The group with higher PAC levels had a lower percentage of current smokers but higher blood pressure levels compared to the group with lower PAC levels. Regarding laboratory tests, the higher PAC level group showed significantly higher levels of PTH, 24-hour urine potassium, 24-hour urine calcium, PAC, PRA, and the aldosterone-renin ratio (ARR). In contrast, serum potassium, serum calcium, and serum phosphorus levels were lower in this group. Additionally, this group had a significantly higher prevalence of PA and was more likely to be using diuretics and beta-blockers. Importantly, among the groups, the higher group also had a higher prevalence of urinary stones and their subtypes compared to the lower PAC group (Figure 2). Moreover, when we further grouped participants according to whether they had urinary stones or not, the result obtained was still that participants with urinary stones had a higher PAC (Table 2).

Relationship Between PAC and Urinary Stones and Its Subtypes

First, we performed a univariate regression analysis, which revealed a strong association between lower PAC and the risk of urinary stones and their subtypes (Table S3). Subsequently, the results from the multifactorial logistic regression analysis reinforced this finding, indicating that PAC levels are closely linked to the occurrence of urinary stones. In Model 1, the risk of urinary stones increased by 21% for every 5-ng/dL increase in PAC (odds ratio [OR], 1.21; 95%

Table 1 Characteristics of the Study Population Based on PAC Quartiles

Characteristic N	Q1 8791	Q2 8790	Q3 8790	Q4 8790	P value
Age (years)	52.32±12.88	51.66±11.78	50.79±12.37	49.68±12.44	<0.001
Sex (%)					0.015
Female	3721 (42.33%)	3772 (42.91%)	3697 (42.06%)	3892 (44.28%)	
Male	5070 (57.67%)	5018 (57.09%)	5093 (57.94%)	4898 (55.72%)	
Current smoking (%)	3104 (35.31%)	3017 (34.32%)	2980 (33.90%)	2641 (30.05%)	<0.001
Current drinking (%)	2771 (31.52%)	2776 (31.58%)	2780 (31.63%)	2574 (29.28%)	0.001
BMI (kg/m^2)	26.88±3.68	26.92±3.64	26.94±3.60	26.97±3.61	0.382
SBP (mmHg)	146.17±18.47	145.96±18.17	154.57±19.36	157.73±19.65	<0.001
DBP (mmHg)	88.31±13.73	88.10±13.55	92.26±14.20	94.30±14.54	<0.001
Medical history					
PA (%)	957 (10.89%)	1300 (14.79%)	1436 (16.34%)	1611 (18.33%)	<0.001
DM (%)	1524 (17.34%)	1386 (15.77%)	1319 (15.01%)	1409 (16.03%)	<0.001
Dyslipidemia (%)	1678 (19.09%)	1688 (19.20%)	1758 (20.00%)	1541 (17.53%)	<0.001
CHD (%)	935 (10.64%)	795 (9.04%)	746 (8.49%)	767 (8.73%)	<0.001
Cancer (%)	156 (1.77%)	110 (1.25%)	110 (1.25%)	144 (1.64%)	0.005
Laboratory tests					
Cr (umol/L)	64.99±14.67	65.10±14.52	65.09±14.63	65.53±14.80	0.070
eGFR (mL/min/1.73 m^2)	114.15 ±27.37	115.29 ± 25.43	116.37 ± 27.05	117.46 ± 27.42	<0.001
BUN (mmol/L)	5.05±1.35	5.04±1.34	5.05±1.36	5.07±1.36	0.541
PTH (pg/mL)	52.56 (41.78–65.84)	52.59 (41.70–66.10)	54.81 (43.58–68.37)	56.82 (44.73–71.16)	<0.001
Serum potassium (mmol/L)	3.82±0.34	3.82±0.34	3.63±0.32	3.51±0.32	<0.001
Serum calcium (mmol/L)	2.27±0.11	2.27±0.11	2.15±0.11	2.09±0.11	<0.001
Serum phosphorus (mmol/L)	1.12±0.18	1.12±0.18	1.07±0.19	1.04±0.18	<0.001
24-h urinary potassium (mmol/L)	36.71±13.82	36.70±14.34	38.88±15.86	39.73±15.38	<0.001
24-h urinary calcium (mmol/L)	4.28 (2.95–5.90)	4.36 (2.96–6.00)	4.35 (3.00–6.05)	4.60 (3.17–6.31)	<0.001
24-h urinary phosphorus (mmol/L)	16.39 (12.09–21.38)	16.54 (12.12–21.39)	16.52 (12.18–21.54)	16.50 (12.17–21.44)	0.516
24-h urinary sodium (mmol/L)	132.99 (94.62–180.31)	133.87 (94.86–180.75)	133.06 (94.88–178.67)	133.51 (95.84–180.12)	0.544
FPG (mmol/L)	5.07±1.12	5.04±1.09	5.02±1.08	5.06±1.12	0.011
TSH (uIU/mL)	2.15 (1.47–3.21)	2.15 (1.45–3.19)	2.17 (1.47–3.19)	2.12 (1.45–3.14)	0.358
PRA (ng/mL/h)	1.97 (0.83–3.06)	1.94 (0.83–3.06)	2.00 (0.87–3.18)	2.09 (0.91–3.28)	<0.001
PAC (ng/dL)	10.09±1.63	12.88±0.65	16.25±1.33	23.84±4.11	<0.001
ARR	5.27 (3.25–11.77)	6.69 (4.20–15.62)	8.13 (5.14–18.82)	11.60 (7.24–25.81)	<0.001
Medications					
Statins (%)	1104 (12.56%)	1022 (11.63%)	976 (11.10%)	916 (10.42%)	<0.001
Aspirins (%)	1122 (12.76%)	1053 (11.98%)	949 (10.80%)	922 (10.49%)	<0.001
Diuretics (%)	892 (10.15%)	897 (10.20%)	949 (10.80%)	1049 (11.93%)	<0.001
Beta-blockers (%)	1670 (19.00%)	1539 (17.51%)	1485 (16.89%)	1531 (17.42%)	0.002
Calcium channel blockers (%)	4506 (51.26%)	4517 (51.39%)	4626 (52.63%)	4927 (56.05%)	<0.001
ACEIs/ARBs (%)	4238 (48.21%)	4022 (45.76%)	3951 (44.95%)	4018 (45.71%)	<0.001
Antihyperglycemic drugs (%)	801 (9.11%)	707 (8.04%)	610 (6.94%)	653 (7.43%)	<0.001
Outcome					
Urinary calculus	821 (9.34%)	946 (10.76%)	1100 (12.51%)	1196 (13.61%)	<0.001
Kidney stone	742 (8.44%)	869 (9.89%)	1002 (11.40%)	1084 (12.33%)	<0.001
Ureter stone	95 (1.08%)	106 (1.21%)	133 (1.51%)	147 (1.67%)	0.002

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or as numbers, and percentages.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PA, primary aldosteronism; DM, diabetes mellitus; CHD, coronary heart disease; Cr, creatinine; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; PTH, parathyroid hormone; FPG, fasting plasma glucose; TSH, thyroid stimulating hormone; PRA, plasma renin activity; ARR, aldosterone-renin ratio; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

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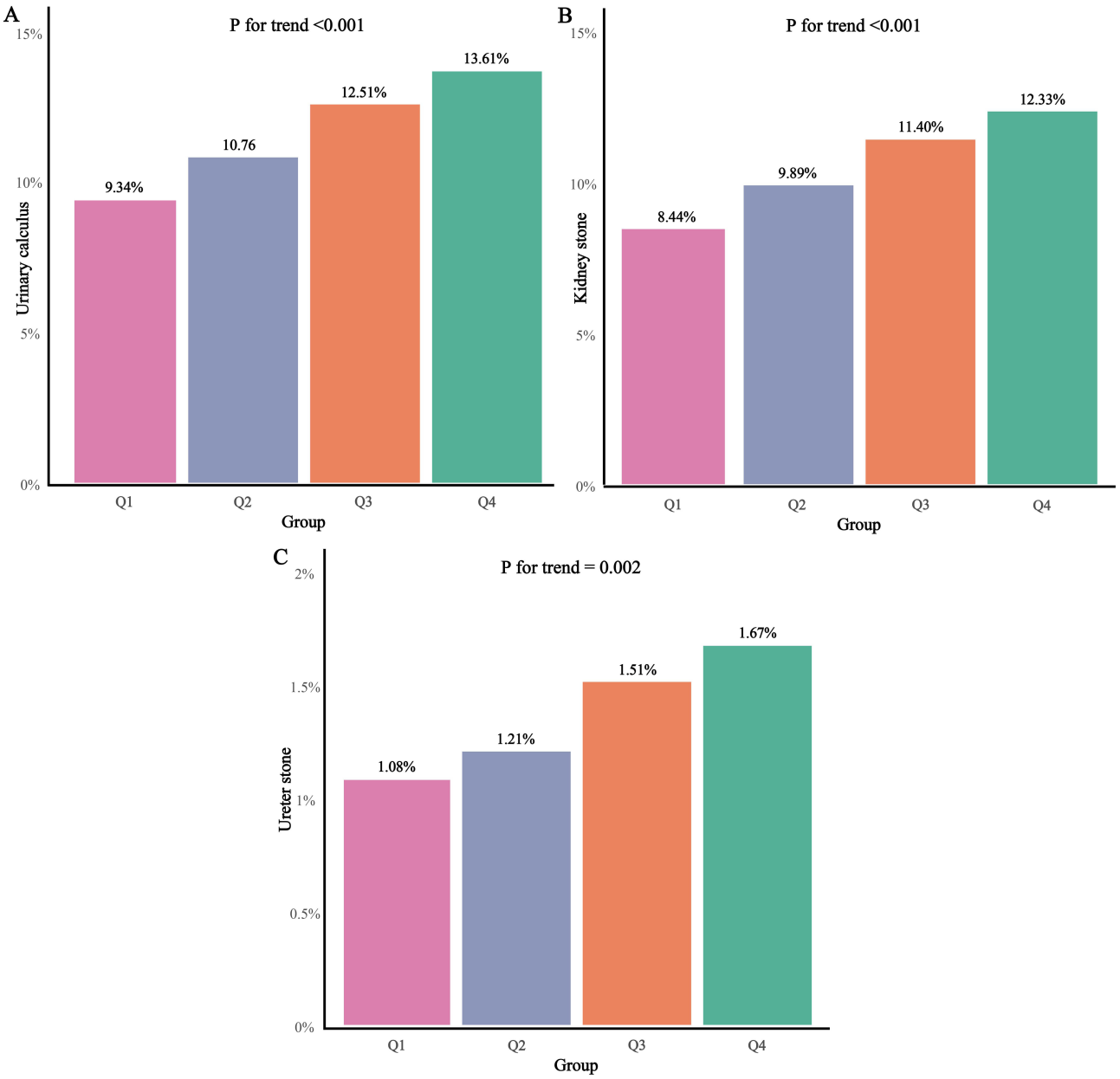

Figure 2 Prevalence of urinary stones and its subtypes after grouping according to PAC quartiles (**A**), Urinary stones; (**B**), Kidney stone; (**C**),Ureter stone.

confidence interval [CI], 1.18–1.24). These results remained stable in the fully adjusted Model 5, where the risk of urinary stones increased by 26% for every 5-ng/dL increase in PAC (OR, 1.26; 95% CI, 1.22–1.30) (Table 3). Similarly, when PAC was converted into categorical variables, the results remained consistent. Specifically, in Model 5, compared

Table 2 Comparison of Characteristics Between Urinary Stones and Non-Urinary Stones Groups

Characteristic N	Non-urinary Calculus 31098	Urinary Calculus 4163	P value
Age (years)	51.13±12.42	51.00±12.38	0.524
Sex (%)			0.284
Female	13371 (43.00%)	1711 (42.11%)	
Male	17727 (57.00%)	2352 (57.89%)	

(*Continued*)

Table 2 (Continued).

Characteristic N	Non-urinary Calculus 31098	Urinary Calculus 4163	P value
Current smoking (%)	10,360 (33.31%)	1382 (34.01%)	0.373
Current drinking (%)	9594 (30.85%)	1307 (32.17%)	0.088
BMI (kg/m2)	26.92±3.63	27.02±3.62	0.102
SBP (mmHg)	151.05±19.61	151.51±19.67	0.166
DBP (mmHg)	90.73±14.28	90.87±14.07	0.559
Medical history			
PA (%)	4676 (15.04%)	628 (15.46%)	0.482
DM (%)	4991 (16.05%)	647 (15.92%)	0.838
Dyslipidemia (%)	5966 (19.18%)	699 (17.20%)	0.002
CHD (%)	2898 (9.32%)	345 (8.49%)	0.086
Cancer (%)	471 (1.51%)	49 (1.21%)	0.125
Laboratory tests			
Cr (umol/L)	65.09±14.64	65.82±14.73	0.003
BUN (mmol/L)	5.05±1.35	5.07±1.35	0.277
PTH (pg/mL)	53.87 (42.50–67.30)	58.20 (45.95–72.99)	<0.001
Serum potassium (mmol/L)	3.70±0.36	3.58±0.32	<0.001
Serum calcium (mmol/L)	2.28±0.13	2.16±0.11	<0.001
Serum phosphorus (mmol/L)	1.09±0.19	1.07±0.17	0.024
24-h urinary potassium (mmol/L)	36.08 (28.42–45.18)	38.37 (29.71–46.44)	<0.001
24-h urinary calcium (mmol/L)	4.30 (2.96–5.94)	5.38 (4.03–7.02)	<0.001
24-h urinary phosphorus (mmol/L)	16.46 (12.11–21.43)	16.60 (12.29–21.47)	0.866
24-h urinary sodium (mmol/L)	133.56 (95.08–180.11)	131.97 (94.93–179.42)	0.205
FPG (mmol/L)	5.05±1.10	5.04±1.10	0.896
TSH (uIU/mL)	2.15 (1.46–3.19)	2.12 (1.45–3.17)	0.713
PRA (ng/mL/h)	2.00 (0.85–3.12)	2.05 (0.91–3.24)	0.046
PAC (ng/dL)	14.61±5.55	16.93±6.24	<0.001
ARR	16.59±34.20	17.48±33.03	0.118
Medications			
Statins (%)	3565 (11.46%)	453 (11.15%)	0.554
Aspirins (%)	3579 (11.51%)	467 (11.49%)	0.978
Diuretics (%)	3338 (10.73%)	449 (11.05%)	0.54
Beta-blockers (%)	5540 (17.81%)	685 (16.86%)	0.134
Calcium channel blockers (%)	16,421 (52.80%)	2155 (53.04%)	0.777
ACEIs/ARBs (%)	14,290 (45.95%)	1939 (47.72%)	0.033
Antihyperglycemic drugs (%)	2438 (7.84%)	333 (8.20%)	0.428

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or as numbers, and percentages.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PA, primary aldosteronism; DM, diabetes mellitus; CHD, coronary heart disease; Cr, creatinine; BUN, blood urea nitrogen; PTH, parathyroid hormone; FPG, fasting plasma glucose; TSH, thyroid stimulating hormone; PRA, plasma renin activity; ARR, aldosterone-renin ratio; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Table 3 Relationship Between PAC and Urinary Stones and Its Subtypes

Exposure	Model 1	Model 2	Model 3	Model 4	Model 5
	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
Urinary stone					
PAC (per 5-ng/dL increase)	1.21 (1.18, 1.24) <0.001	1.21 (1.18, 1.25) <0.001	1.26 (1.22, 1.30) <0.001	1.26 (1.22, 1.30) <0.001	1.26 (1.22, 1.30) <0.001

(*Continued*)

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Table 3 (Continued).

Exposure	Model 1	Model 2	Model 3	Model 4	Model 5
	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P	OR (95% CI) P
Quartiles of PAC					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	1.17 (1.06, 1.29) 0.001	1.17 (1.06, 1.29) 0.001	1.17 (1.06, 1.29) 0.001	1.17 (1.06, 1.29) 0.001	1.17 (1.06, 1.29) 0.001
Q3	1.39 (1.26, 1.53) <0.001	1.39 (1.26, 1.53) <0.001	1.45 (1.31, 1.61) <0.001	1.45 (1.31, 1.61) <0.001	1.45 (1.31, 1.61) <0.001
Q4	1.53 (1.39, 1.68) <0.001	1.53 (1.40, 1.69) <0.001	1.64 (1.46, 1.84) <0.001	1.64 (1.46, 1.84) <0.001	1.64 (1.47, 1.84) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
Kidney stone					
PAC (per 5-ng/dL increase)	1.21 (1.18, 1.24) <0.001	1.21 (1.18, 1.25) <0.001	1.26 (1.22, 1.30) <0.001	1.26 (1.22, 1.30) <0.001	1.26 (1.22, 1.31) <0.001
Quartiles of PAC					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	1.19 (1.07, 1.32) 0.001	1.19 (1.07, 1.32) 0.001	1.19 (1.07, 1.32) 0.001	1.19 (1.07, 1.32) 0.001	1.19 (1.07, 1.32) 0.001
Q3	1.40 (1.26, 1.54) <0.001	1.40 (1.26, 1.54) <0.001	1.46 (1.31, 1.63) <0.001	1.46 (1.31, 1.63) <0.001	1.47 (1.31, 1.64) <0.001
Q4	1.53 (1.38, 1.68) <0.001	1.53 (1.38, 1.68) <0.001	1.65 (1.46, 1.86) <0.001	1.64 (1.46, 1.85) <0.001	1.65 (1.46, 1.86) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001
Ureter stone					
PAC (per 5-ng/dL increase)	1.34 (1.25, 1.43) <0.001	1.37 (1.28, 1.47) <0.001	1.50 (1.38, 1.63) <0.001	1.50 (1.38, 1.63) <0.001	1.50 (1.38, 1.63) <0.001
Quartiles of PAC					
Q1	Reference	Reference	Reference	Reference	Reference
Q2	1.12 (0.85, 1.48) 0.435	1.12 (0.85, 1.48) 0.409	1.13 (0.85, 1.49) 0.408	1.12 (0.85, 1.49) 0.421	1.12 (0.84, 1.47) 0.445
Q3	1.41 (1.08, 1.84) 0.011	1.43 (1.08, 1.84) 0.008	1.56 (1.17, 2.08) 0.003	1.55 (1.16, 2.07) 0.003	1.54 (1.15, 2.06) 0.004
Q4	1.56 (1.20, 2.02) <0.001	1.67 (1.21, 2.04) <0.001	1.91 (1.40, 2.63) <0.001	1.90 (1.38, 2.61) <0.001	1.87 (1.36, 2.58) <0.001
P for trend	<0.001	<0.001	<0.001	<0.001	<0.001

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, smoking status, and drinking status were adjusted.Model 3: Model 2 plus adjustment for PA, DM, CHD, Dyslipidemia, and cancer.Model 4: Model 3 plus adjustment for Cr, BUN, TSH, FPG, serum potassium, serum calcium, serum phosphorus, 24-h urinary potassium, 24-h urinary calcium,24-h urinary phosphorus, eGFR, and PTH.Model 5: Model 4 plus adjustment for use of statins, aspirin, diuretics, beta-blockers, calcium channel blockers, ACEIs/ARBs, and antihyperglycemic drugs.
Abbreviations: PAC, plasma aldosterone concentration; OR, odds ratio; CI, confidence interval.
Other abbreviations, see Table 1.

to group Q1, groups Q2, Q3, and Q4 had OR values of 1.17 (95% CI, 1.06–1.29), 1.45 (95% CI, 1.31–1.61), and 1.64 (95% CI, 1.47–1.84), respectively. These findings were also consistent for the subtypes of KS and US (Table 3).

Furthermore, we used RCS to explore the dose-response relationship between PAC and urinary stones and their subtypes. The results indicated that the risk of urinary stones and its subtypes KS and US significantly increased when PAC levels exceeded 14.2 ng/dL, 14 ng/dL, and 14.5 ng/dL, respectively (Figure 3). Similarly, a two-stage comparative analysis based on the turning points identified by the RCS revealed that participants with PAC levels greater than 14.2 ng/dL had a 50% increased risk compared to those with PAC levels of 14.2 ng/dL or less (Table 4). Among the subtypes of KS and US, participants with PAC levels above the tipping points also exhibited a significantly higher risk of disease compared to those with PAC levels below or equal to the tipping points (Table 4).

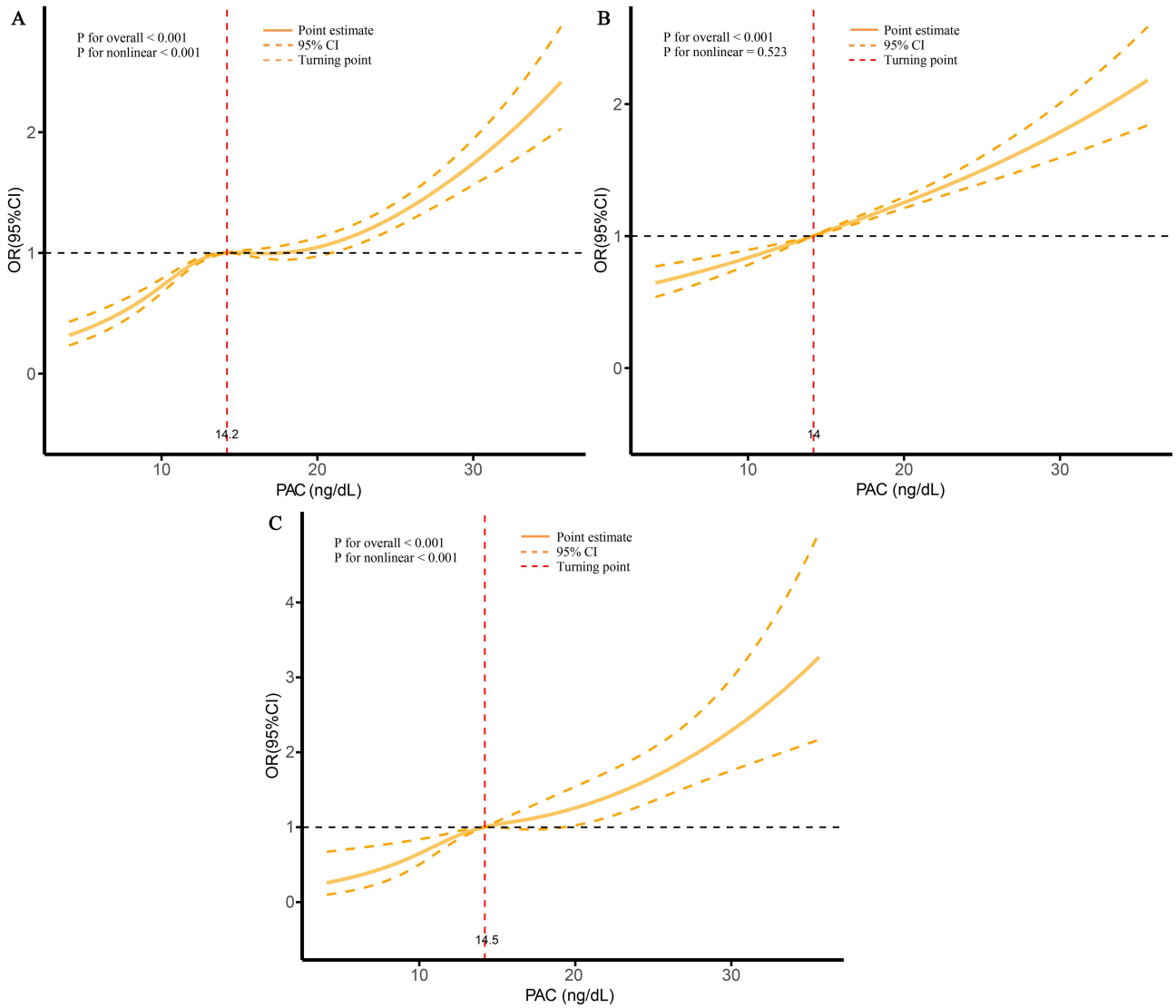

Figure 3 Dose-response association between PAC and urinary stones and its subtypes (**A**), Urinary stones; (**B**), Kidney stone; (**C**),Ureter stone.

To further evaluate the importance of PAC in the occurrence of urinary stones and their subtypes (KS and US), we performed Boruta variable importance analysis based on a random forest logistic regression model. This analysis showed that PAC was a more significant variable compared to others (Figure 4), further supporting our findings that PAC may play a critical role in the development of urinary stones.

Table 4 Two-Stage Comparative Analysis of the Relationship Between PAC and Urinary Stones and Its Subtypes Based on the RCS Turning Points

Exposure	Model 1 OR (95% CI) P	Model 2 OR (95% CI) P	Model 3 OR (95% CI) P	Model 4 OR (95% CI) P	Model 5 OR (95% CI) P
Urinary stone					
Turning point (ng/dL)	14.2	14.2	14.2	14.2	14.2
<= 14.2	Reference	Reference	Reference	Reference	Reference
> 14.2	1.41 (1.32, 1.51) <0.001	1.41 (1.32, 1.51) <0.001	1.50 (1.38, 1.63) <0.001	1.50 (1.38, 1.63) <0.001	1.50 (1.38, 1.63) <0.001

(*Continued*)

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Table 4 (Continued).

Exposure	Model 1 OR (95% CI) P	Model 2 OR (95% CI) P	Model 3 OR (95% CI) P	Model 4 OR (95% CI) P	Model 5 OR (95% CI) P
Kidney stone					
Turning point (ng/dL)	14	14	14	14	14
<= 14	Reference	Reference	Reference	Reference	Reference
> 14	1.36 (1.27, 1.45) <0.001	1.36 (1.27, 1.46) <0.001	1.42 (1.31, 1.55) <0.001	1.42 (1.30, 1.51) <0.001	1.41 (1.32, 1.55) <0.001
Ureter stone					
Turning point (ng/dL)	14.5	14.5	14.5	14.5	14.5
<= 14.5	Reference	Reference	Reference	Reference	Reference
> 14.5	1.98 (1.64, 2.41) <0.001	2.07 (1.71, 2.52) <0.001	2.64 (2.09, 3.34) <0.001	2.63 (2.09, 3.33) <0.001	2.62 (2.08, 3.32) <0.001

Notes: Model 1: no covariates were adjusted. Model 2: age, sex, BMI, smoking status, and drinking status were adjusted.Model 3: Model 2 plus adjustment for PA, DM, CHD, Dyslipidemia, and cancer.Model 4: Model 3 plus adjustment for Cr, BUN, TSH, FPG, serum potassium, serum calcium, serum phosphorus, 24-h urinary potassium, 24-h urinary calcium,24-h urinary phosphorus, eGFR, and PTH.Model 5: Model 4 plus adjustment for use of statins, aspirin, diuretics, beta-blockers, calcium channel blockers, ACEIs/ARBs, and antihyperglycemic drugs.
Abbreviations: PAC, plasma aldosterone concentration; OR, odds ratio; CI, confidence interval.
Other abbreviations, see Table 1.

Subgroup Analysis

Since our study population consisted solely of hypertensive patients, we considered that different baseline conditions and medication use might influence the study's results. Therefore, we first stratified the participants based on sex, age, BMI, smoking status, drinking status, CHD, DM, PRA, and ARR. The results indicated that, regardless of the stratification, the increase in PAC levels remained strongly associated with the occurrence of urinary stones and its subtypes (Figure 5). We then performed a secondary stratification based on drug use, and the results were consistent with the overall findings, further confirming that our conclusions were not influenced by these stratification factors (Figure 6).

Sensitivity Analysis

To further ensure the robustness of our results, we conducted several sensitivity analyses. First, considering that cancer patients often use various antitumor drugs and may experience bone destruction, along with calcium and phosphorus loss, we excluded participants with cancer. The results remained consistent with the overall findings (Table S4). Second, recognizing that diuretics might have a preventive effect on urinary stones, we excluded participants who were taking diuretics, and the results were stable (Table S5). Additionally, because patients with PA typically have elevated PAC levels, which could increase the risk of urinary stones, we excluded participants with PA. Again, the results remained unchanged (Table S6). Finally, to address the potential influence of unmeasured confounders, we performed an E-value analysis, which indicated that these unmeasured factors were insufficient to alter our findings (Table S7).

Discussion

Our study is consistent with previous studies that found an increased risk of kidney stones in patients with PA. However, in this study, we discovered a groundbreaking relationship between PAC and urinary stones in hypertensive patients. Elevated PAC levels were significantly associated with the development of urinary stones, including KS and US. This association remained robust even after adjusting for potential confounding factors, such as age, gender, and comorbidities. Furthermore, threshold analysis demonstrated that the risk of urinary stone formation increases markedly when PAC levels exceed 14.2 ng/dL. Notably, variable importance analysis revealed that PAC holds greater predictive significance compared to other clinical variables, underscoring its pivotal role in urinary stone pathogenesis. This finding suggests that maintaining PAC within a reasonable range can help prevent the occurrence of urinary stones and may provide new insights for future treatment development.

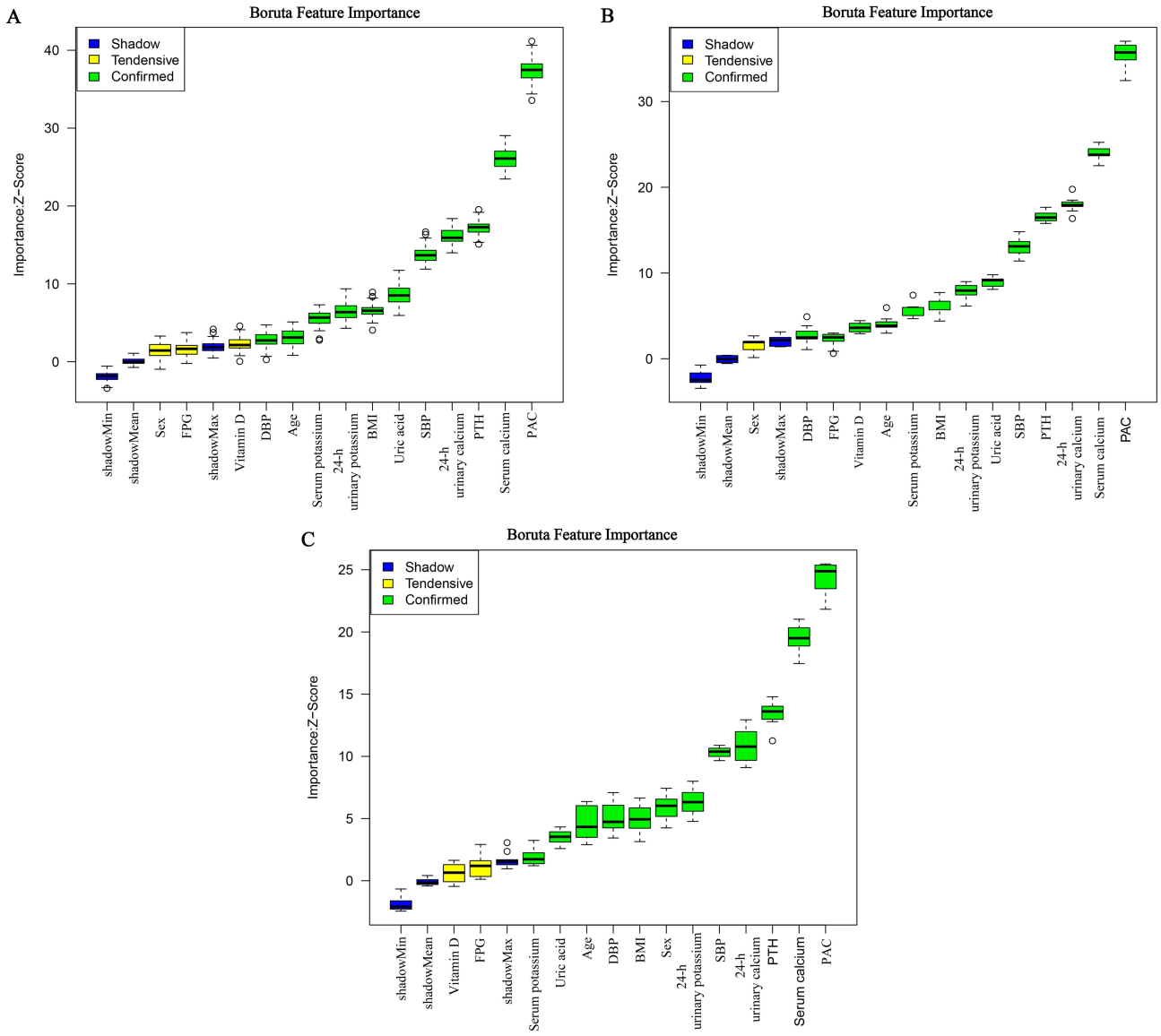

Figure 4 Boruta variable importance (**A**), Urinary stones; (**B**), Kidney stone; (**C**),Ureter stone.

Urinary stones, especially KS, are common chronic urologic diseases that are often difficult to cure and prone to recurrence.[30,31] Initially, the stones are small or confined to the kidneys and do not cause any symptoms. However, when the stones become large and numerous, they can impair kidney function.[4,32] In addition, when smaller stones enter the ureter, they may cause severe renal colic due to ureteral obstruction.[33,34] If these obstructing stones are not removed, they may lead to hydronephrosis and acute renal failure.[35–37] The long-term presence of these stones in the urinary system leads to chronic inflammation in the urinary tract, which can result in urinary tract infections or, in severe cases, sepsis.[38,39] Furthermore, long-term stone retention can damage the mucosa of the urinary tract and increase the risk of developing urinary tumors.[40,41] Therefore, given the serious impact of urinary stones on health, early prevention and treatment are particularly important.

Hypertension is one of the most common chronic diseases. The prevalence of hypertension is expected to rise further as living standards, life stress, and life expectancy increase.[42,43] Reports indicate that nearly one-third of the world's population suffers from hypertension.[42,44,45] Previous studies have suggested that the risk of KS is significantly higher in hypertensive patients compared to normal subjects, which raises the possibility that effective blood pressure control may reduce the risk of KS.[46,47] Similarly, PA, the main type of secondary hypertension, is associated with a variety of diseases

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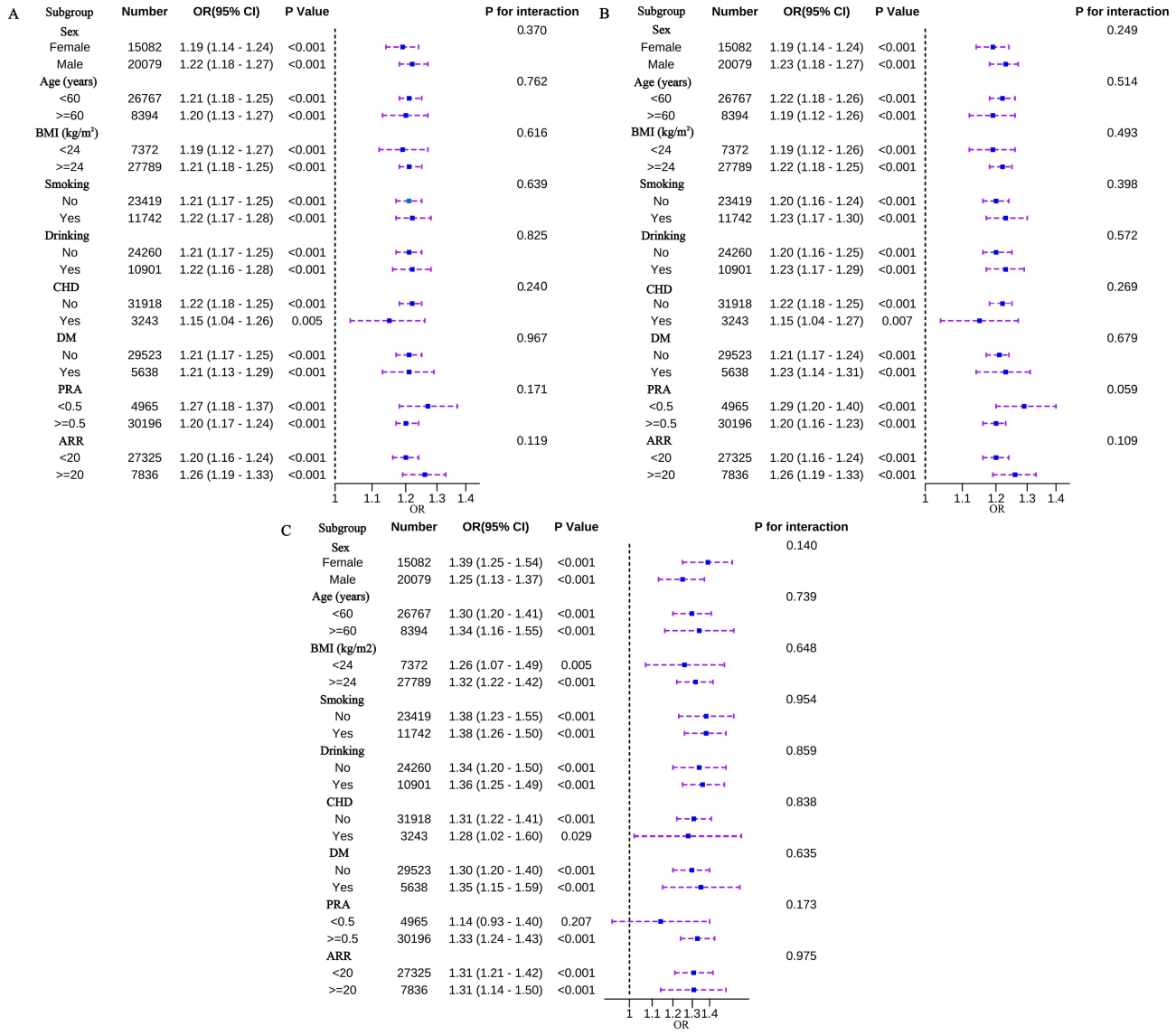

Figure 5 Subgroup analysis after grouping according to basic status (**A**), Urinary stones; (**B**), Kidney stone; (**C**),Ureter stone.

and may increase the risk of kidney deterioration.[48–50] Interestingly, some studies also found that people with PA were more likely to develop KS.[25,51,52] Since aldosterone is the main diagnostic indicator of PA, there is an urgent need to clarify its role in urinary stones in all hypertensive patients.

Aldosterone, an important salt-corticoid hormone in the maintenance of ionic homeostasis, has been identified in many previous studies as having potential effects in calcium regulation.[27,53,54] First, one study found that aldosterone increased urinary calcium excretion in mice, leading to loss of blood calcium.[24] There was also a close relationship between aldosterone and PTH, with PTH levels increasing as aldosterone levels increased.[55,56] Second, another study found a bidirectional positive physiologic effect between aldosterone and PTH.[56] One hypothesis is that long-term high aldosterone exposure increases the secretion of PTH, which further increases blood calcium, and that high blood calcium levels (mainly due to increased bone and intestinal calcium absorption) increase glomerular filtration load, overloading tubule reabsorption, and thus induce hypercalcemia.[57,58] Subsequently, parathyroid hormone potentiates the aldosterone response to angiotensin II, and the parathyroid hormone receptor is expressed in aldosterone-producing cells.[59,60] Moreover, in a study of the relationship between plasma aldosterone concentrations and bone mineral density, it was demonstrated that increasing urinary calcium with increasing aldosterone concentrations resulted in a continuous loss of

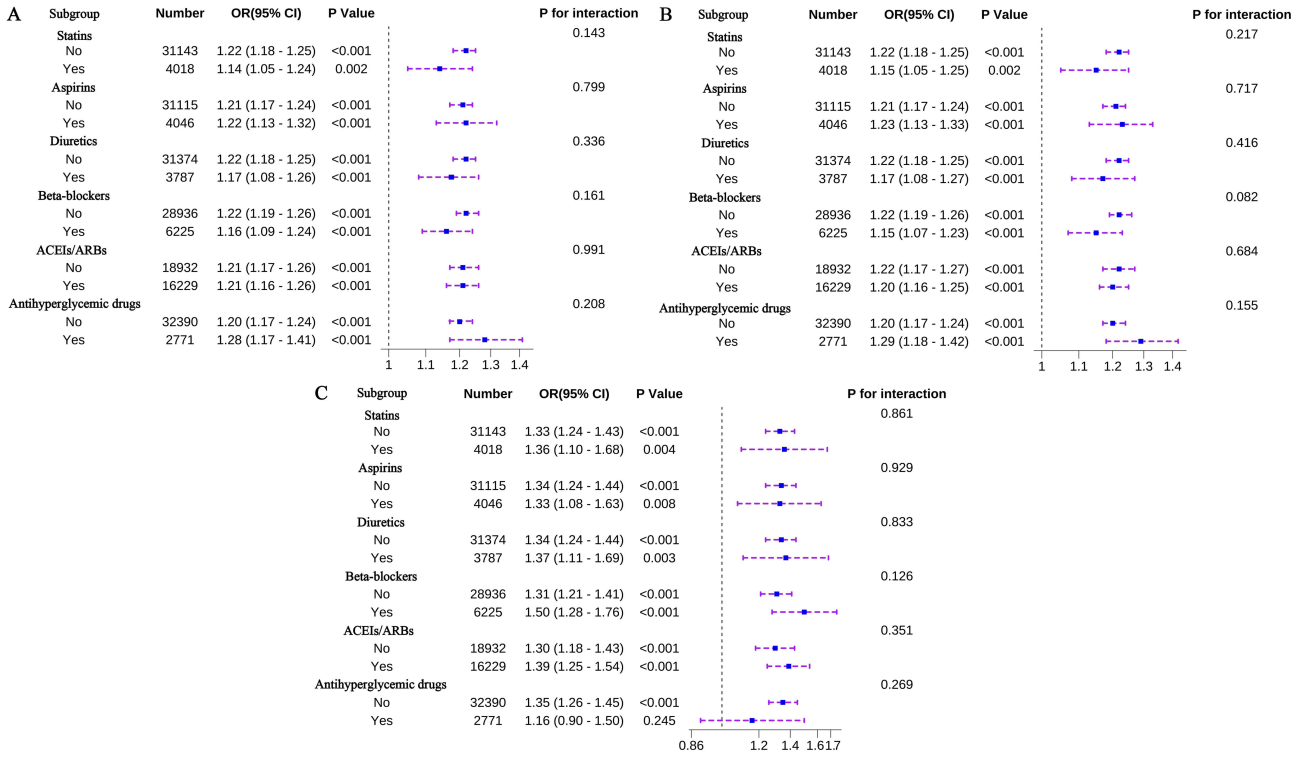

Figure 6 Subgroup analysis after grouping according to different drug types (**A**), Urinary stones; (**B**), Kidney stone; (**C**), Ureter stone.

bone mass, with an increased risk of osteoporosis and fractures.[27,61,62] This evidence confirms that aldosterone is an important cause of hypercalcemia. The present study further reveals the relationship between PAC and urinary stones, showing that the high urinary calcium loss caused by elevated aldosterone may be an important factor leading to the development of urinary stones in hypertensive patients. In addition, the study further found that the risk of urinary stones was further increased when PAC exceeded the threshold of 14.2ng/dL, which may have important clinical significance for the prevention and intervention of urinary stones in hypertensive patients in the future.

This study, based on a large-scale population analysis, is the first to elucidate the relationship between PAC levels and urinary stones, including its subtypes, among a substantial cohort of hypertensive patients. These findings may hold significant clinical implications for the prevention and treatment of urinary stones in hypertensive populations in the future. However, this study acknowledges several limitations. First, due to the cross-sectional design, we cannot establish a causal relationship between PAC levels and urinary calculus. Future longitudinal studies are necessary to further validate these findings. Second, the study participants were exclusively from northern China, which may limit the generalizability of the results to other regions. Caution is advised when extrapolating these findings to broader populations. Additionally, the lack of detailed data on dietary habits and micronutrient intake represents another limitation, as these factors may influence urinary stone formation. Moreover, our study lacked data on urinary stone composition, preventing assessment of whether PAC levels differentially influence specific stone types. Future studies incorporating stone composition analysis are needed to clarify these relationships. Finally, although we adjusted for numerous potential confounders in our regression analysis, the possibility of unmeasured confounders cannot be entirely ruled out. Nevertheless, the results of our E-value analysis suggest that the observed associations are robust and unlikely to be easily disproven.

Conclusion

This study, based on a large-scale cross-sectional analysis, is the first to demonstrate that elevated PAC levels in hypertensive patients are strongly associated with the development of urinary stones and their subtypes. Notably, the risk of urinary stone formation increases significantly when PAC levels exceed 14.2 ng/dL. These findings suggest that

PAC may play a critical role in the pathogenesis of urinary stones in hypertensive patients. Therefore, maintaining PAC levels within a lower range could potentially reduce the risk of urinary stone formation, offering significant clinical implications. Furthermore, this study may provide a novel perspective for future research and therapeutic strategies aimed at preventing and managing urinary stones in this population. Of course, more prospective randomized controlled trials may be needed to further confirm these findings.

Data Sharing Statement

The datasets used and/or analyzed in this study are available from the corresponding author on request if necessary.

Institutional Review Board Statement

The study received approval from the Ethics Committee of the Xinjiang Uygur Autonomous Region People's Hospital (KY2022080904), and written informed consent was obtained from all participants involved in the research.

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Disclosure

The authors disclose no conflicts of interest.

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