International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

# Serum Metallome Features and Their Effects on Chronic Kidney Disease: A Comparative Study

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Video Abstract

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**Objective:** Epidemiological evidence links exposure to certain metals with decreased kidney function and kidney disease progression. This study investigates the metallome profiles in chronic kidney disease (CKD) patients and their relationship to disease onset and progression.

**Methods:** A total of 341 CKD patients (CKD group) and 60 healthy controls (HC group) were recruited. Renal function markers, including urea, creatinine (Creat), uric acid (UA), cystatin C (CysC), and complement component 1q (C1q), along with the levels of 26 metal elements, were assessed to examine the relationship between metal element concentrations and renal function markers.

**Results:** Compared to the HC group, serum concentrations of Li, Mg, Al, Ca, V, Mn, Ni, Cu, Ga, Se, Rb, Mo, Sn, Cs, and Pb were elevated in CKD patients (all $P<0.05$), while Co, Hg, and U levels were reduced (all $P<0.05$). Serum concentrations of Li, Al, V, Mo, Sn, Cs, and Hg correlated with renal function markers (Urea $|r|=0.146$ to $0.545$, Creat $|r|=0.120$ to $0.584$, CysC $|r|=0.132$ to $0.641$; all $P<0.05$). Logistic regression identified Al, V, Co, Ga, Cs, and Pb as independent predictors of CKD onset (all $P<0.05$), while Li, V, Mo, and Cs were linked to disease progression (all $P<0.05$). Strong positive correlations were observed between Al and V ($r=0.821$), Al and Ga ($r=0.717$), and V and Ga ($r=0.646$), while Co negatively correlated with Al ($r=-0.449$), V ($r=-0.410$), and Ga ($r=-0.288$).

**Conclusion:** CKD patients exhibit altered serum levels of various metals. Al, V, Co, Ga, Cs, and Pb are linked to CKD onset, while Li, V, Mo, and Cs relate to its progression. These findings suggest that monitoring specific metal elements like V, Pb and Mo could aid in early CKD detection and progression assessment.

**Keywords:** metallome, metabolic profiles, chronic kidney disease, ultra-high performance liquid chromatography-tandem mass spectrometry

## Introduction

In recent decades, there has been a significant increase in both the incidence and mortality of chronic kidney disease (CKD).[1] In 2021, the age-standardized death rate for CKD reached 18.5%, ranking it as the 11th leading cause of death globally and the 7th among non-communicable diseases.[2] The disability and mortality rates associated with CKD are increasing at the fastest pace among all chronic diseases. Projections suggest that CKD may become the fifth leading cause of death worldwide by 2040.[3] Due to its high prevalence and limited awareness, many patients do not receive early detection and treatment. Consequently, by the time of diagnosis, a decline in glomerular filtration rate (GFR) often occurs. Without effective intervention, CKD progresses to end-stage kidney disease (ESKD), leaving patients reliant on dialysis or kidney transplantation for survival. This progression, along with the resulting economic and healthcare burdens, positions CKD as a major global health challenge.

Trace elements, although present in minute quantities, are essential for numerous physiological processes. They contribute to the metabolism of enzymes and bioactive molecules, playing a key role in maintaining the homeostasis of the internal environment. However, elevated levels of these elements can result in an increase in free radicals, leading to

Received: 19 April 2025
Accepted: 17 September 2025
Published: 1 October 2025

cellular damage and potential cell death. Research has demonstrated that an excess of metal ions is instrumental in metal-dependent cell death.[3] The metallome comprises metal- and metalloid-containing proteins, enzymes, and other biomolecules, as well as free metal and metalloid ions, within cells, organs, or tissues. In essence, the metallome includes all metal-associated species within a biological system.[4] The application of metallome profiling has been explored in cancer, thyroid disorders, leukemia, and neurodegenerative diseases.[5–8] However, its role in CKD remains underexplored. Almeida et al[9] previously identified an elevated risk of trace element imbalance in patients undergoing maintenance hemodialysis, with both hemodialysis and kidney transplantation increasing the likelihood of renal cell carcinoma and urethral cancer in ESKD patients.[10] Additionally, Zhou et al[11–13] highlighted the involvement of ferroptosis in the progression of various kidney conditions, including acute kidney injury, CKD, and renal fibrosis. This study aimed to investigate the serum metabolic profile in CKD patients, assess the relationship between metallome element levels and renal function markers, and explore the influence of these elements on CKD onset and progression, with the goal of identifying potential risk factors for disease onset and progression. While prior studies focused on individual metals, this study presents a comprehensive analysis of the entire metallome (26 elements) in CKD, revealing novel associations with disease onset and progression.

# Materials and Methods

## Participants and Grouping

A total of 341 patients with CKD were enrolled from Mianyang Central Hospital between July and December 2023, comprising 163 males and 178 females, with a mean age of 54.4±14.9 years. The control group consisted of 60 healthy individuals (HC group) who underwent routine physical examinations during the same period, including 26 males and 34 females, with a mean age of 51.2±13.0 years. The study protocol received approval from the hospital ethics committee (approval number: P2020030), and all participants were fully informed about the study objectives and procedures, subsequently providing written informed consent.

## Inclusion Criteria

CKD group:

1) Age ≥ 18 years, 2) Female participants not pregnant or breastfeeding, 3) Diagnosis of CKD according to the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines,[1] 4) No use of medications, nutritional, or health supplements in the 3 months preceding the study, 5) No history of systemic malignancies.

HC group:

Healthy individuals aged ≥ 18 years, who had undergone a physical examination within the past month, with normal liver and kidney function, blood analysis, and urinalysis results.

## Exclusion Criteria

1) Non-compliance with sample collection protocols, 2) Pregnant or breastfeeding women, 3) Use of medications, nutritional, or health supplements in the 3 months prior to the study, 4) History of nephrectomy, 5) Presence of other systemic malignancies.

## Sample Size

The experimental design was structured into five distinct study groups (N=5), comprising a healthy control group, a hypertensive nephropathy group, a diabetic kidney disease group, a lupus nephritis group, and a kidney cancer group (group statistics are detailed in a separate publication). To determine the appropriate sample size, the PASS software version 15.0 (NCSS LLC, Kaysville, Utah, USA) was utilized within the mean multiple comparison module, employing a significance level of α=0.05 and a power of 1-β=0.90. The sample size for each group was established at a 1:1 ratio, requiring 56 participants per group. Given that this study did not include follow-up with participants and there were no instances of subject dropout, the final sample size for each group was confirmed to be no fewer than 56 cases.

# Methods

## Sample Collection

Venous blood was collected in the early morning after an overnight fast of 8 to 12 hours, using BD Vacutainer vacuum blood collection tubes (ordinary, preservative-free, BD Company, USA), to a volume of approximately 5 mL. The sample was allowed to stand at room temperature for 30 minutes to allow for coagulation, followed by centrifugation at 3000 rpm for 15 minutes to separate the serum. A 1.5 mL aliquot was transferred to a low-adsorption centrifuge tube (Aicor, Taizhou, Zhejiang) and stored at −80°C for subsequent metallome element analysis. The remaining sample was analyzed for renal function markers within 2 hours.

## Assays of Renal Function Markers

Renal function markers were analyzed using a LABOSPECT 008α fully automatic biochemical analyzer (Hitachi, Japan). The assays performed included urease-glutamate dehydrogenase for urea (Urea), sarcosine oxidase for creatinine (Creat), uricase for uric acid (UA), latex immunoturbidimetry for cystatin C (CysC), and for complement component 1q (C1q). All kits, except for the C1q kit (Zybio, Chongqing, China), were sourced from Maccura Biotechnology (Chengdu, China). Estimated GFR (eGFR) was calculated using the CKD-EPI 2021 equation for eGFRCreat-CysC.[14]

## Assays of Metallome Elements

Serum levels of 26 metallome elements, including calcium (Ca), Magnesium (Mg), Copper (Cu), Zinc (Zn), Ferrum (Fe), Manganese (Mn), Selenium (Se), Lead (Pb), Cadmium (Cd), Aluminium (Al), Chromium (Cr), Germanium (Ge), Molybdenum (Mo), Cobalt (Co), Vanadium (V), Stannum (Sn), Nickel (Ni), Arsenic (As), Lithium (Li), Hydrargyrum (Hg), Uranium (U), Gallium (Ga), Rubidium (Rb), Argentum (Ag), Cesium (Cs) and Aurum (Au), were quantified using the 7850 Inductively Coupled Plasma Mass Spectrometry (ICP-MS) system (Agilent, USA). The tuning and mixed internal standard solutions for the analysis were sourced from Agilent Technologies (China) Co., Ltd. (Beijing, China), while the multi-element calibration standard solution was obtained from the China National Nonferrous Metals and Electronic Materials Analysis and Testing Center (Beijing, China). Test results below 0.001 μg/L were recorded as <0.001 μg/L.

## Statistical Analysis

Normality of the data was assessed using the Shapiro–Wilk test. Data conforming to a normal distribution were presented as mean ± standard deviation (x ± s), with ANOVA applied for multiple-group comparisons and one-way ANOVA for pairwise analysis. Non-normally distributed data were presented as median (interquartile range) [M (P25, P75)], with non-parametric tests (eg, Mann–Whitney *U*-test, Spearman correlation analysis) employed for group comparisons. The correlation is categorized as follows based on the value of the correlation coefficient: no correlation ($\leq 0.1$), poor correlation ($> 0.1$ to 0.3), mild correlation ($> 0.3$ to 0.5), moderate correlation ($> 0.5$ to 0.7), strong correlation ($> 0.7$ to 0.9), and extremely strong correlation ($> 0.9$). Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Furthermore, PASS software version 15.0 (NCSS LLC, Kaysville, Utah, USA) was employed for the estimation of sample size and the analysis of power. $P < 0.05$ considered statistically significant.

# Results

## Demographic Data, Serum Kidney Function, and Metal Levels

The renal function and metabolic profiles of the subjects were presented in Table 1. Gender and age did not significantly differ between the CKD and HC groups ($P>0.05$), but differences were noted across eGFR grades ($P<0.05$). Compared to the HC group, the CKD group exhibited statistically significant alterations in renal function markers, including Urea, Creat, UA, CysC, C1q, and eGFR (all $P<0.05$). Among the 26 metabolic parameters analyzed, 15 elements, including Li, Mg, Al, Ca, V, Mn, Ni, Cu, Ga, Se, Rb, Mo, Sn, Cs, and Pb, were elevated, while 4 elements, namely Co, Ag, Hg, and U, were reduced (all $P<0.05$). No significant changes were observed for Fe, Zn, As, and Cd (all $P>0.05$). Furthermore, the concentrations of Cr, Ge, and Au in both groups were below the detection limit of 0.001 μg/L, recorded as <0.001 μg/L,

**Table 1** Demographic Data, Kidney Function and Metallome Elements Levels of The Study Subjects

| Variable | CKD (n=341) | HC (n=60) | $\chi^2$/t /Z | *P* |
|---|---|---|---|---|
| **Demographic data** | | | | |
| Sex (n, Male / Female) | 163/178 | 26/34 | 0.41 | 0.523 |
| Age (years, Mean ± SD) | 54.4±14.9 | 51.2 ± 13.0 | −1.54 | 0.124 |
| **Kidney Function** | | | | |
| Urea(mg/L), M (P25, P75) | 7.09(5.15, 12.23) | 4.53(3.59, 5.44) | 64.569 | <0.001 |
| Creat(μmol/L), M (P25, P75) | 100.8(69.7, 190.8) | 60.3(52.2, 71.4) | 70.240 | <0.001 |
| UA(μmol/L), M (P25, P75) | 369.6(297.9, 448.0) | 287.7(238.4, 332.8) | 35.267 | <0.001 |
| CysC(mg/L), M (P25, P75) | 1.40(1.05, 2.39) | 0.85(0.82, 0.93) | 94.261 | <0.001 |
| C1q(mg/L), M (P25, P75) | 180.0(155.5, 209.0) | 188.0(175.3, 211.0) | 4.126 | 0.042 |
| eGFR(mL/min/$1.73m^2$), M (P25, P75) | 53.8(24.7, 83.3) | 107.1(98.6, 113.7) | 101.445 | <0.001 |
| **eGFR staging (mL/min/$1.73m^2$)** | | | 167.20 | <0.001 |
| G1(eGFR≥90), n(%) | 59 (17.30) | – | | |
| G2(60≤eGFR<90), n(%) | 100 (29.33) | – | | |
| G3(30≤eGFR<60), n(%) | 84 (24.63) | – | | |
| G4(15≤eGFR<30), n(%) | 41 (12.02) | – | | |
| G5(eGFR<15), n(%) | 57 (16.72) | – | | |
| **Metallome Elements Levels** | | | | |
| Li(μg/L), M (P25, P75) | 0.710(0.001, 1.622) | 0.261(0.001, 0.644) | 11.467 | 0.001 |
| Mg(μg/L), M (P25, P75) | 9570 (7434, 12,167) | 7597 (6743, 9057) | 18.108 | <0.001 |
| Al(μg/L), M (P25, P75) | 60.26(14.57, 136.45) | 21.97(0.001, 41.71) | 30.123 | <0.001 |
| Ca(μg/L), M (P25, P75) | 39,246 (31,758, 47,922) | 34,182(29,488, 39,496) | 14.394 | <0.001 |
| V(μg/L), M (P25, P75) | 0.116(0.028, 0.21) | 0.001(0.001, 0.016) | 71.981 | <0.001 |
| Cr(μg/L), M (P25, P75) | <0.001 (NA) | <0.001 (NA) | – | – |
| Mn(μg/L), M (P25, P75) | 0.379(0.001, 0.884) | 0.001(0.001, 0.136) | 29.186 | <0.001 |
| Fe(μg/L), M (P25, P75) | 363.7 (193.5, 570.6) | 415.7(313.3, 601.7) | 3.362 | 0.067 |
| Co(μg/L), M (P25, P75) | 0.001(0.001, 0.151) | 0.276(0.001, 0.473) | 26.975 | <0.001 |
| Ni(μg/L), M (P25, P75) | 0.527(0.127, 1.056) | 0.307(0.133, 0.48) | 13.168 | <0.001 |
| Zn(μg/L), M (P25, P75) | 238.5(170.1, 319.9) | 265.4(210.9, 319.6) | 2.624 | 0.105 |
| Cu(μg/L), M (P25, P75) | 423.3(297.0, 581.8) | 332.2 (254.5, 434.7) | 11.619 | 0.001 |
| Ga(μg/L), M (P25, P75) | 0.014(0.001, 0.062) | 0.001(0.001, 0.009) | 22.325 | <0.001 |
| Ge(μg/L), M (P25, P75) | <0.001 (NA) | <0.001 (NA) | – | – |
| As(μg/L), M (P25, P75) | 0.001(0.001, 0.353) | 0.056(0.001, 0.198) | 0.149 | 0.700 |
| Se(μg/L), M (P25, P75) | 36.4 (24.0, 53.0) | 24.6 (17.9, 32.4) | 23.660 | <0.001 |
| Rb(μg/L), M (P25, P75) | 63.4(45.6, 86.8) | 48.3(33.4, 60.9) | 21.570 | <0.001 |
| Mo(μg/L), M (P25, P75) | 1.51(0.99, 2.51) | 0.94(0.84, 1.12) | 37.326 | <0.001 |
| Ag(μg/L), M (P25, P75) | 0.001(0.001, 0.001) | 0.056(0.033, 0.115) | 161.603 | <0.001 |
| Cd(μg/L), M (P25, P75) | 0.114(0.047, 0.200) | 0.117(0.072, 0.168) | 0.013 | 0.908 |
| Sn(μg/L), M (P25, P75) | 0.375(0.181, 0.630) | 0.178(0.093, 0.276) | 21.797 | <0.001 |
| Cs(μg/L), M (P25, P75) | 0.825(0.625, 1.111) | 0.537(0.416, 0.694) | 42.230 | <0.001 |
| Au(μg/L), M (P25, P75) | <0.001 (NA) | <0.001 (NA) | – | – |
| Hg(μg/L), M (P25, P75) | 0.001(0.001, 0.025) | 0.244(0.194, 0.322) | 103.941 | <0.001 |
| Pb(μg/L), M (P25, P75) | 0.588(0.32, 1.132) | 0.261(0.126, 0.387) | 37.174 | <0.001 |
| U(μg/L), M (P25, P75) | 0.195(0.115, 0.364) | 0.356(0.295, 0.524) | 39.020 | <0.001 |

**Abbreviation**: NA, Not applicable.

and were considered statistically insignificant, thus excluded from further analysis. These results suggest that disruptions in serum metal element metabolism may be a characteristic feature of CKD.

## Metabolic Profile and Renal Function

Spearman correlation analysis was conducted to evaluate the relationship between serum metabolic profiles and renal function markers in CKD patients. Correlations between the levels of metallome elements and renal function markers were assessed

(Supplementary Table 1). The correlation coefficients (r) and p-values for both the CKD and HC groups were used to generate a heat map via Origin software (2024) (Figure 1). In the CKD group, statistically significant correlations were found between the metal elements Li, Al, V, Ni, Ga, Mo, Ag, Sn, Cs, Hg, Pb and Urea (|r|=0.146–0.545, all *P*<0.05); between Li, Al, Ca, V, Se, Mo, Sn, Cs, Hg, Pb, U and Creat (|r|=0.120–0.584, all *P*<0.05); and between Li, Co, Mo, Cs, U and UA (|r|=0.129–0.305, all *P*<0.05). Significant correlations were also observed between Li, Al, V, Ni, Se, Mo, Sn, Cs, Hg, Pb, U and CysC (|r|=0.132–0.641, all *P*<0.05); Al and Cu showed statistically significant associations with C1q (|r|=0.131–0.155, all *P*<0.05). No significant correlations were observed for Mg, Mn, and Rb with any of the renal function markers (|r|=0.001–0.081, all *P*>0.05). Among the elements in the HC group, significant correlations were observed between Hg, Rb, and Creat (|r|=0.262–0.280, all *P*<0.05); between Al and UA (|r|=0.269, *P*<0.05); and between Mg, Mo, Hg, Pb, and CysC (|r|=0.258–0.337, all *P*<0.05). Additionally, correlations between Mn, Co, Hg, and C1q were significant (|r|=0.276–0.404, all P<0.05). No significant correlations were found between any elements and Urea (|r|=0.006–0.224, all *P*>0.05). In CKD patients, serum levels of multiple metallome elements were altered compared to the HC group. Li, Mo, and Cs exhibited positive correlations with renal function markers, excluding C1q (r=0.168–0.641, all *P*<0.05), while Al, V, and Sn were positively correlated with Urea, Creat, and CysC (r=0.120–0.268, all *P*<0.05). These results suggest that the serum metabolic profile in CKD patients is altered and correlates with renal function markers to varying extents.

## Correlation Between Metallome Elements and CKD Onset and Progression

### Correlation Between Metallome Elements and CKD Onset

To investigate the correlation between metallome elements and CKD onset, a collinearity test was first conducted on the levels of 19 metallome elements differing between the CKD and HC groups (Supplementary Table 2). Variance inflation factors for Mg and Ca were 5.559 and 9.054, respectively, suggesting potential collinearity.[15] Consequently, these elements were excluded from further analysis. Binary logistic regression was performed on the remaining 17 elements, with 15 elements showing a univariate P-value <0.05, which were subsequently included in multivariate regression (Table 2). The analysis identified Al, V, Co, Ga, Cs, and Pb as independent factors influencing CKD onset (all *P*<0.05). Among these, Al (OR=1.01), V (OR=1.52), Ga (OR=1.59), Cs (OR=1.03), and Pb (OR=1.04) were identified as risk factors for CKD onset, while Co (OR=0.03) was found to be protective. These results indicate that although serum levels of numerous elements are altered in CKD patients (19 elements were observed in this study), only a select few—Al, V, Co, Ga, Cs, and Pb in this study—directly impact CKD onset. Alterations in other elements may be influenced by the renal function of CKD patients.

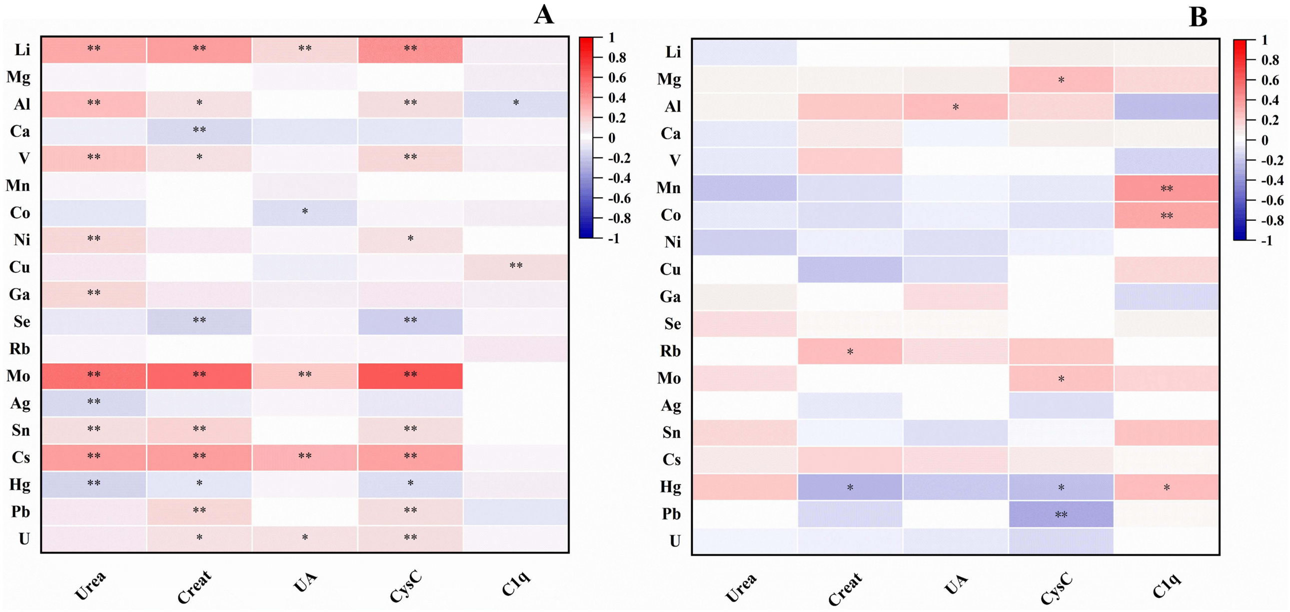

**Figure 1** Hot Spot Map of Correlation between Metallome elements and Renal Function Indicators. (**A**) CKD group. (**B**) HC group. White, not relevant (r=0.00). Red, positive correlation (r>0.00). Blue, negative correlation (r<0.00). **P*<0.05; ***P*<0.01.

**Table 2** The Effect of Metallome Elements on CKD Occurrence

| Variable | Single Factor | | | | | | Multi-Factor | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β | S.E | Z | *P* | OR (95% CI) | Power | β | S.E | Z | *P* | OR (95% CI) | Power |
| Li | 0.85 | 0.23 | 3.79 | <0.001 | 2.35 (1.51 ~ 3.65) | 1.000 | 0.43 | 0.44 | 0.93 | 0.334 | 1.54(0.64 ~ 3.68) | 0.470 |
| Al | 0.02 | 0.00 | 4.62 | <0.001 | 1.02 (1.01 ~ 1.03) | 0.038 | 0.42 | 0.09 | 22.11 | <0.001 | 1.01 (1.01 ~ 1.02) | 0.028 |
| V | 0.27 | 0.05 | 5.50 | <0.001 | 1.32 (1.19 ~ 1.45) | 0.715 | 0.42 | 0.09 | 22.11 | <0.001 | 1.52(1.27 ~ 1.80) | 0.447 |
| Mn | 2.40 | 0.57 | 4.24 | <0.001 | 11.07(3.64 ~ 33.68) | 1.000 | 0.01 | 0.01 | 1.97 | 0.160 | 1.01(0.99 ~ 1.03) | 0.028 |
| Co | −2.49 | 0.55 | −4.54 | <0.001 | 0.08 (0.03 ~ 0.24) | 1.000 | −3.48 | 1.02 | 11.64 | 0.001 | 0.03(0.00 ~ 0.23) | 1.000 |
| Ni | 1.45 | 0.37 | 3.86 | <0.001 | 4.25 (2.04 ~ 8.87) | 1.000 | −0.61 | 0.49 | 1.57 | 0.211 | 0.54(0.21 ~ 1.41) | 0.767 |
| Cu | 2.28 | 0.76 | 2.99 | 0.003 | 9.80 (2.19 ~ 43.80) | 1.000 | −0.89 | 1.75 | 0.26 | 0.611 | 0.41(0.01 ~ 12.63) | 0.973 |
| Ga | 0.40 | 0.10 | 3.93 | <0.001 | 1.49 (1.22 ~ 1.82) | 0.951 | 0.46 | 0.20 | 5.35 | 0.021 | 1.59(1.07 ~ 2.35) | 0.525 |
| Se | 0.04 | 0.01 | 4.43 | <0.001 | 1.04 (1.02 ~ 1.06) | 0.055 | 0.03 | 0.02 | 1.67 | 0.196 | 1.03(0.99 ~ 1.07) | 0.034 |
| Rb | 0.03 | 0.01 | 4.38 | <0.001 | 1.03 (1.01 ~ 1.04) | 0.046 | −0.01 | 0.02 | 0.18 | 0.670 | 0.99(0.96 ~ 1.03) | 0.028 |
| Mo | 1.42 | 0.31 | 4.57 | <0.001 | 4.13 (2.25 ~ 7.60) | 1.000 | 0.82 | 0.46 | 3.10 | 0.078 | 2.26(0.91 ~ 5.60) | 0.945 |
| Ag | −0.01 | 0.25 | −0.04 | 0.966 | 0.99 (0.61 ~ 1.60) | 0.031 | - | - | - | - | - | - |
| Sn | 0.28 | 0.27 | 1.05 | 0.295 | 1.33 (0.78 ~ 2.26) | 0.738 | - | - | - | - | - | - |
| Cs | 3.09 | 0.62 | 4.98 | <0.001 | 22.03(6.52 ~ 74.42) | 1.000 | 0.03 | 0.01 | 5.86 | 0.015 | 1.03(1.00 ~ 1.05) | 0.034 |
| Hg | −0.44 | 0.18 | −2.43 | 0.015 | 0.65 (0.45 ~ 0.92) | 0.974 | 0.00 | 0.00 | 1.41 | 0.235 | 1.00(0.99 ~ 1.00) | 0.028 |
| Pb | 2.27 | 0.47 | 4.89 | <0.001 | 9.71 (3.90 ~ 24.17) | 1.000 | 0.04 | 0.01 | 14.66 | <0.001 | 1.04(1.02 ~ 1.06) | 0.037 |
| U | −0.88 | 0.31 | −2.84 | 0.005 | 0.41 (0.23 ~ 0.76) | 1.000 | −0.59 | 0.58 | 1.04 | 0.308 | 0.55(0.18 ~ 1.73) | 0.742 |

**Abbreviations**: β, regression coefficient. S.E, standard error. OR, Odds Ratio. CI, Confidence Interval.

The power analysis indicates that in single-factor analysis, the power values for Co, Ga, Cs, and Pb exceed 0.8, while the power values for V and Al are 0.715 and 0.038, respectively. In contrast, the multi-factor analysis reveals power values of 1.000 for Co, 0.525 for Ga, 0.447 for V, 0.037 for Pb, 0.034 for Cs, and 0.028 for Al. These findings suggest that, except for Co, which demonstrates a robust independent protective effect against CKD, the power to detect other elements as independent risk factors for the occurrence or progression of CKD is significantly constrained due to mixed interaction effects.

## Impact of Metallome Elements on CKD Progression

To assess the influence of metallome elements on CKD progression, patients were categorized into stages G1 to G5 according to the KDIGO clinical practice guidelines.[1] Based on the CKD stage distribution, the levels of 17 metallome elements (excluding Mg and Ca due to potential collinearity) were compared between the CKD and HC groups. Ordered logistic regression identified 9 elements with $P<0.05$ in univariate analysis, which were subsequently included in multivariate regression (Table 3). The analysis revealed that Li (OR=1.28), V (OR=1.01), Mo (OR=2.28), and Cs (OR=2.84) were independent risk factors for CKD progression ($P<0.05$). To further clarify the role of these four elements, their levels were re-

**Table 3** The Effects of Metallome Elements on CKD Development

| Variable | Single Factor | | | | | Multi-Factor | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | β | S.E | t | *P* | OR (95% CI) | β | S.E | t | *P* | OR (95% CI) |
| Li | 0.57 | 0.08 | 6.68 | <0.001 | 1.76 (1.49 ~ 2.08) | 0.25 | 0.09 | 6.73 | 0.009 | 1.28(1.06 ~ 1.54) |
| Al | 0.01 | 0.00 | 4.03 | <0.001 | 1.01 (1.01 ~ 1.01) | 0.00 | 0.00 | 0.02 | 0.885 | 1.00 (1.00 ~ 1.00) |
| V | 0.01 | 0.00 | 4.97 | <0.001 | 1.01 (1.01 ~ 1.01) | 0.03 | 0.01 | 4.74 | 0.029 | 1.03(1.00 ~ 1.06) |
| Mn | −0.09 | 0.06 | −1.44 | 0.151 | 0.91 (0.80 ~ 1.03) | - | - | - | - | - |
| Co | 0.20 | 0.47 | 0.43 | 0.669 | 1.22 (0.49 ~ 3.07) | - | - | - | - | - |
| Ni | 0.30 | 0.13 | 2.39 | 0.017 | 1.36 (1.06 ~ 1.74) | −0.09 | 0.14 | 0.41 | 0.522 | 0.91(0.70 ~ 1.20) |

(*Continued*)

**Table 3** (Continued).

| Variable | Single Factor | | | | | Multi-Factor | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | β | S.E | t | *P* | OR (95% CI) | β | S.E | t | *P* | OR (95% CI) |
| Cu | 0.00 | 0.00 | 0.28 | 0.780 | 1.00 (1.00 ~ 1.00) | - | - | - | - | - |
| Ga | 0.01 | 0.00 | 3.98 | <0.001 | 1.01 (1.01 ~ 1.01) | 0.00 | 0.03 | 0.00 | 0.949 | 1.00 (0.94 ~ 1.06) |
| Se | −0.02 | 0.00 | −3.67 | <0.001 | 0.98 (0.98 ~ 0.99) | −0.01 | 0.00 | 3.32 | 0.068 | 0.99(0.98 ~ 1.00) |
| Rb | −0.00 | 0.00 | −1.33 | 0.185 | 1.00 (0.99 ~ 1.00) | - | - | - | - | - |
| Mo | 1.00 | 0.10 | 10.14 | <0.001 | 2.72 (2.24 ~ 3.30) | 0.82 | 0.10 | 70.47 | <0.001 | 2.27(1.88 ~ 2.75) |
| Ag | 0.15 | 0.16 | 0.93 | 0.354 | 1.16 (0.85 ~ 1.59) | - | - | - | - | - |
| Sn | −0.01 | 0.13 | −0.08 | 0.937 | 0.99 (0.77 ~ 1.28) | - | - | - | - | - |
| Cs | 1.99 | 0.30 | 6.65 | <0.001 | 7.30 (4.06 ~ 13.11) | 0.01 | 0.00 | 11.44 | 0.001 | 1.01(1.00 ~ 1.02) |
| Hg | −0.26 | 0.16 | −1.61 | 0.108 | 0.77 (0.57 ~ 1.06) | - | - | - | - | - |
| Pb | 0.21 | 0.09 | 2.27 | 0.023 | 1.23 (1.03 ~ 1.47) | 0.00 | 0.00 | 3.03 | 0.082 | 1.00 (1.00 ~ 1.00) |
| U | 0.13 | 0.26 | 0.51 | 0.613 | 1.14 (0.68 ~ 1.90) | - | - | - | - | - |

**Abbreviations**: β, regression coefficient. S.E, standard error. OR, Odds Ratio. CI, Confidence Interval.

evaluated using univariate ordered logistic regression, with stage G1 as the reference (Table 4). The results indicated that, compared to G1, Li and Mo levels affected stages G2 to G5 (all $P<0.05$). The magnitude of this impact intensified with the progression of CKD, as evidenced by the sequential increase in OR values: for Li, the ORs were 1.62, 1.79, 1.83, and 2.14, respectively; for Mo, the ORs were 4.75, 8.16, 11.77, and 16.43, respectively. Cs levels influenced stages G3 to G5 (all $P<0.05$), with OR values of 3.85, 8.72, and 5.01, respectively. While V levels affected only stage G5 (OR=1.04, $P<0.05$). Further analysis of the correlation between Li, V, Mo, and Cs levels and eGFR in the CKD group, adjusted for age and gender, was conducted using Zstats v1.0 software to generate the Restricted Cubic Spline (RCS) curve (Figure 2). The findings indicated a nonlinear dose-response relationship between these elements and eGFR levels, contributing to CKD progression.

## Prediction of CKD Onset and Progression by Metallome Elements

### Prediction of CKD Onset

To assess the predictive value of six metallome elements (Al, V, Co, Ga, Cs, and Pb) in CKD onset, Receiver Operating Characteristic (ROC) analysis was performed to evaluate diagnostic performance (Table 5 and Figure 3A). AUC values were classified as follows: 0.50≤AUC<0.60 (unqualified), 0.60≤AUC<0.70 (poor), 0.70≤AUC<0.80 (fair), 0.80≤AUC<0.90 (good), and AUC≥0.90 (excellent).[16] The results indicated that among the observed elements, V exhibited the highest predictive value for CKD onset, with an AUC (95% CI) of 0.841 (0.799–0.884), sensitivity of 0.710, and specificity of 0.950. Al, Cs, and Pb demonstrated the second-best predictive value, with AUCs (95% CI) of 0.721 (0.667–0.776), 0.763 (0.695–0.831), and 0.790 (0.734–0.847), respectively. In contrast, Li, Co, Ga, and Cd displayed lower predictive values, all with AUCs<0.70. Analysis of combinations [combining V (AUC>0.80) with Al, Cs, and Pb (0.70<AUC<0.80)] revealed that V combined with Pb resulted in the highest diagnostic performance (AUC=0.931). Further inclusion of additional elements did not enhance diagnostic efficiency (Table 5 and Figure 3B).

### Prediction of CKD Progression

To assess the predictive value of the four metallome elements (Li, V, Mo, and Cs) in CKD progression, the disease was categorized into mild (G1-G3) and severe (G4-G5) stages, using an eGFR threshold of <60 mL/min/1.73$m^2$ as the cutoff.[1] ROC analysis was performed to evaluate diagnostic performance (Table 6 and Figure 4A). The results indicated that Mo exhibited the highest predictive value for severe CKD (AUC=0.813), followed by Cs (AUC=0.701), Li (AUC=0.684), and V (AUC=0.590). Notably, even a combined analysis of all four elements did not surpass the diagnostic accuracy of Mo alone (Table 6 and Figure 4B).

**Table 4** Ordered Logistic Regression Analysis of Metallome Elements Corresponding to the Development of CKD

| **Variable** | **Threshold 1 (G1vs.G2)** | | | | **Threshold 2 (G1vs.G3)** | | | | **Threshold 3 (G1vs.G4)** | | | | **Threshold 4 (G1vs.G5)** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **β±SE** | **χ2** | ***P*** | **OR** | **β±SE** | **χ2** | ***P*** | **OR** | **β±SE** | **χ2** | ***P*** | **OR** | **β±SE** | **χ2** | ***P*** | **OR** |
| Li | 0.48±0.24 | 3.881 | 0.049 | 1.62 | 0.58±0.25 | 5.322 | 0.021 | 1.79 | 0.60±0.27 | 4.941 | 0.026 | 1.83 | 0.76±0.27 | 7.920 | 0.005 | 2.14 |
| V | 0.00±0.02 | 0.018 | 0.892 | 1.00 | 0.01±0.01 | 1.080 | 0.299 | 1.01 | 0.02±0.02 | 2.432 | 0.119 | 1.02 | 0.04±0.02 | 7.098 | 0.008 | 1.04 |
| Mo | 1.56±0.39 | 15.784 | <0.001 | 4.75 | 2.10±0.40 | 27.514 | <0.001 | 8.16 | 2.47±0.41 | 36.228 | <0.001 | 11.77 | 2.80±0.41 | 46.591 | <0.001 | 16.43 |
| Cs | 0.7±0.66 | 1.113 | 0.291 | 2.01 | 1.35±0.68 | 3.928 | 0.047 | 3.85 | 2.17±0.74 | 8.589 | 0.003 | 8.72 | 1.61±0.8 | 4.073 | 0.044 | 5.01 |

**Notes**: G1, eGFR≥90. G2, 60≤eGFR<90. G3, 30≤eGFR<60. G4, 15≤eGFR<30. G5, eGFR<15.

**Abbreviations**: β, regression coefficient; S.E, standard error; OR, Odds Ratio; CI, Confidence Interval.

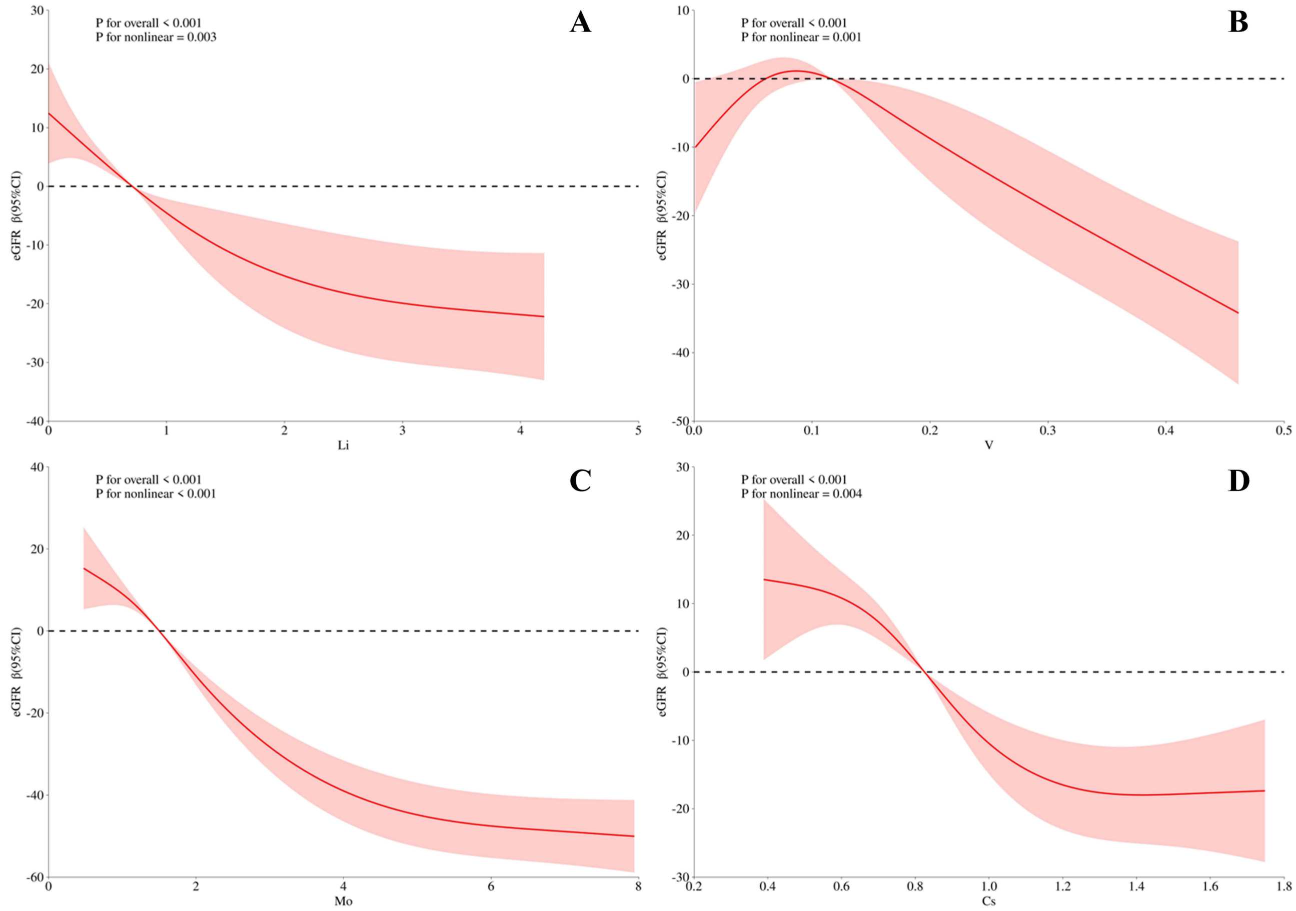

**Figure 2** RCS curves of correlation between Li, V, Mo, Cs and eGFR. Each curve represents the relationship of a specific metal element with eGFR. (**A**) Li and eGFR. (**B**) V and eGFR. (**C**) Mo and eGFR. (**D**) Cs and eGFR.

## Direct Correlation Among Metallome Elements Associated with CKD Onset and Progression

Spearman correlation analysis was conducted to assess the relationship between the levels of the eight metallome elements influencing CKD onset and progression (Supplementary Table 3). A heat map was generated using OriginPro (2024) software, with r and P values presented (Figure 5). The analysis revealed moderate and strong positive correlations between Al and V (r=0.821), Al and Ga (r=0.717), and V and Ga (r=0.646) in the blood of CKD patients. Poor or mild positive correlations were observed for Li and Co (r=0.162), Li and Mo (r=0.341), Li and Co (r=0.367), Al and Mo (r=0.170), V and Mo (r=0.184), Ga and Mo (r=0.116), and Cs and Mo (r=0.335). Poor or mild negative correlations were observed between Al and Co (r=−0.449), V and Co (r=−0.410), Ga and Co (r=−0.288), and Pb and V (r=−0.119), while no significant correlations were found for the remaining elements ($P>0.05$) (Supplementary Table 3). These results suggest a potential synergistic interaction between Al, V, and Ga in the onset and progression of CKD, while these elements may also exhibit antagonistic effects with Co.

## Enrichment and Analysis of Metabolite Pathways Involved in Metallome Elements

KEGG metabolite pathway enrichment analysis was conducted to investigate the involvement of metallome elements in the mechanisms underlying CKD. This analysis focused on six metallome elements associated with CKD onset, using the "Omicsolution" platform (https://www.omicsolu-tion.com/wkomics/main/). A total of 13 enriched pathways were identified (Figure 6A), with only Co and Pb implicated in metabolic processes. The top five pathways, ranked by Background

**Table 5** Diagnostic Performance of Metallome Elements in Predicting CKD Occurrence

| Variable | AUC (95% CI) | Se | Sp | YI |
|---|---|---|---|---|
| Single Element Prediction | | | | |
| Al | 0.721(0.667–0.776) | 0.537 | 0.950 | 0.487 |
| V | 0.841(0.799–0.884) | 0.710 | 0.950 | 0.660 |
| Co | 0.682(0.601–0.762) | 0.768 | 0.617 | 0.385 |
| Ga | 0.683(0.626–0.741) | 0.437 | 0.967 | 0.404 |
| Cs | 0.763(0.695–0.831) | 0.607 | 0.850 | 0.457 |
| Pb | 0.790(0.734–0.847) | 0.710 | 0.950 | 0.660 |
| Collaborative Forecasting | | | | |
| V + Al | 0.855(0.812–0.897) | 0.701 | 0.950 | 0.651 |
| V + Cs | 0.911(0.870–0.953) * | 0.815 | 0.867 | 0.682 |
| V + Pb | 0.931(0.900–0.963) * | 0.798 | 0.933 | 0.731 |
| V + Al + Cs | 0.914(0.872–0.956) * | 0.862 | 0.833 | 0.696 |
| V + Al + Pb | 0.936(0.904–0.967) * | 0.903 | 0.850 | 0.753 |
| V + Cs + Pb | 0.944(0.914–0.973) * | 0.842 | 0.950 | 0.792 |
| V + Al + Cs + Pb | 0.949(0.920–0.977) * | 0.848 | 0.933 | 0.781 |

**Notes**:*Compared with V, the difference of AUC was statistically significant.
**Abbreviations**: AUC, Area Under Curve; CI, Confidence Interval; Se, sensitivity; Sp, specificity; YI, youden index; +, joint.

Ratio value, included ABC transporters, the citric acid cycle (TCA) and respiratory electron transport, metabolism of porphyrins, heme biosynthesis, cadmium-induced DNA synthesis and macrophage proliferation, and metallothionein-metal binding (Table 7). Similarly, analysis of four additional metallome elements influencing CKD development revealed 10 enriched pathways (Figure 6B), with Mo and Li involved in metabolic processes. The top five pathways by Background Ratio value were SLC-mediated transmembrane transport, transport of inorganic cations/anions and

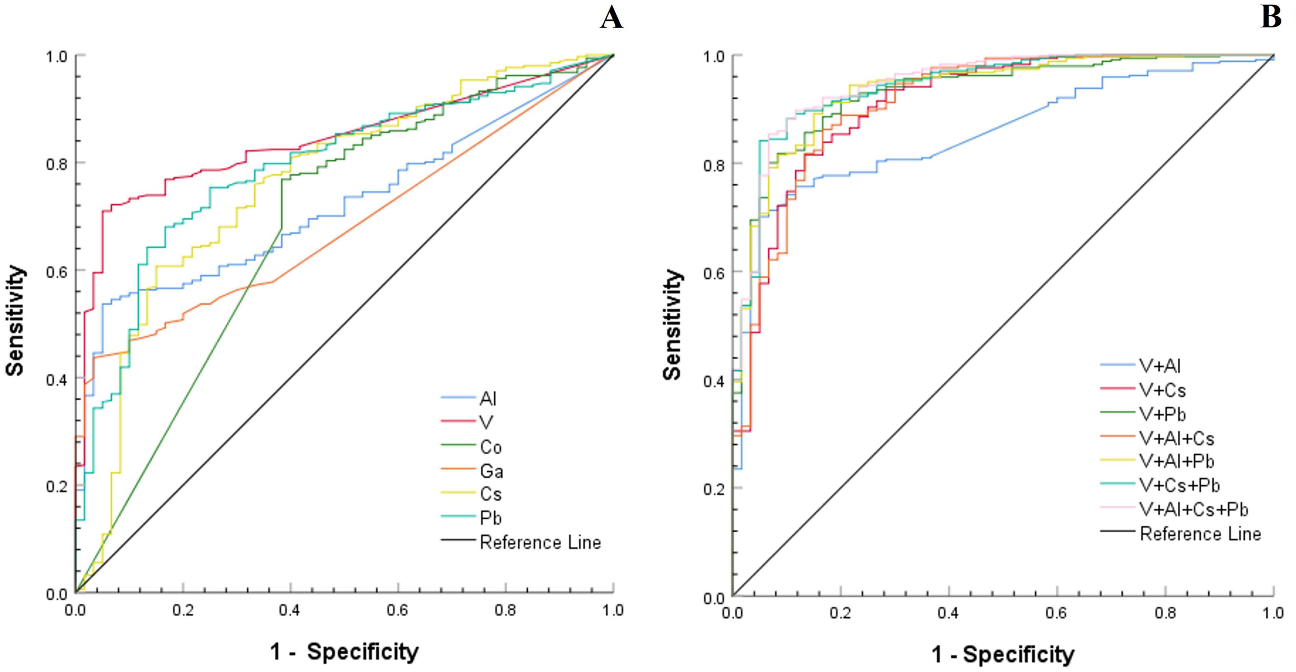

**Figure 3** ROC Curve of Metallome elements in Predicting CKD Occurrence. (**A**) Individual metallome elements predict the occurrence of CKD. (**B**) V combined with Al, Mo, Cs, and Pb predicts the occurrence of CKD.

**Table 6** Diagnostic Performance of Metallome Elements in Predicting Moderate to Severe

| Variable | AUC (95% CI) | Se | Sp | YI |
|---|---|---|---|---|
| Single Element Prediction | | | | |
| Li | 0.684 (0.635–0.736) | 0.522 | 0.774 | 0.296 |
| V | 0.590(0.536–0.643) | 0.517 | 0.698 | 0.215 |
| Mo | 0.813(0.767–0.853) | 0.687 | 0.811 | 0.498 |
| Cs | 0.701(0.649–0.749) | 0.637 | 0.717 | 0.354 |
| Collaborative Forecasting | | | | |
| Mo + Cs | 0.827(0.782–0.866) | 0.626 | 0.887 | 0.513 |
| Mo + Li | 0.826(0.781–0.864) | 0.775 | 0.755 | 0.529 |
| Mo + V | 0.819(0.774–0.858) | 0.681 | 0.817 | 0.499 |
| Mo + Cs + Li | 0.834(0.790–0.872) | 0.709 | 0.824 | 0.533 |
| Mo + Cs + V | 0.830(0.786–0.868) | 0.698 | 0.805 | 0.502 |
| Mo + Cs + Li +V | 0.836(0.793–0.874) | 0.637 | 0.874 | 0.512 |

**Abbreviations**: AUC, Area Under Curve; CI, Confidence Interval; Se, sensitivity; Sp, specificity; YI, youden index; +, joint.

amino acids/oligopeptides, iron uptake and transport, ion channel transport, and sulfate/sulfite metabolism (Table 7). These results suggest that of the eight metallome elements linked to CKD onset and progression, two impact CKD onset by modulating aerobic metabolism, two contribute to disease progression via substance transport, and the remaining four elements potentially influence kidney function through indirect effects on metabolic pathways, which could not be enriched in the relevant pathways.

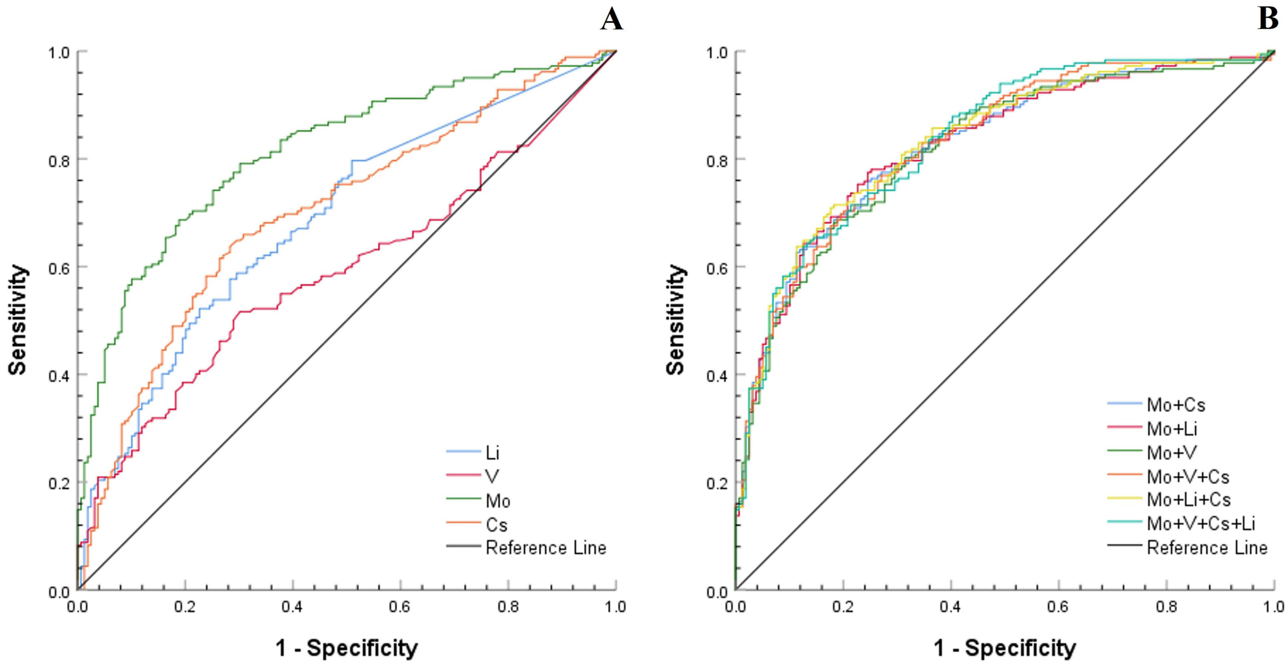

**Figure 4** ROC Curve of Metallome elements in Predicting Moderate to Severe CKD. (**A**) Individual metallome elements predict severe CKD. (**B**) Mo combined with Cs, Li, and V predicts severe CKD.

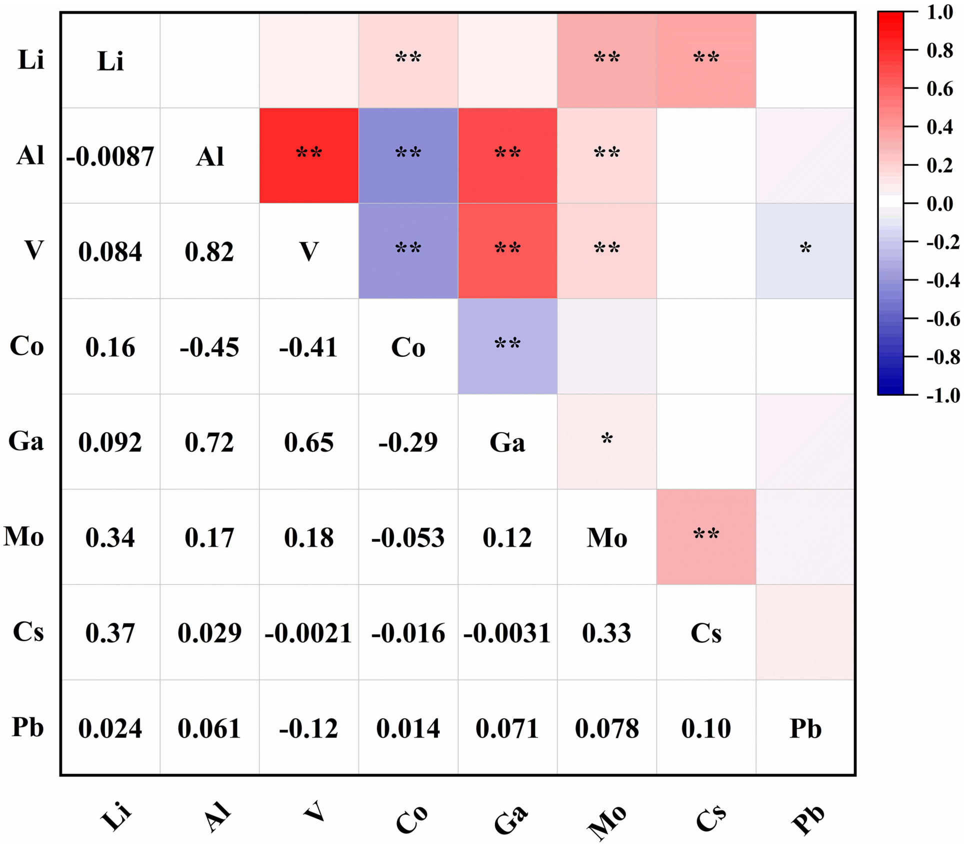

**Figure 5** Hot Spot Map of Correlations Among Metallome elements Affecting CKD. White, not relevant (r=0.00). Red, positive correlation (r>0.00). Blue, negative correlation (r<0.00). *P<0.05; **P<0.01.

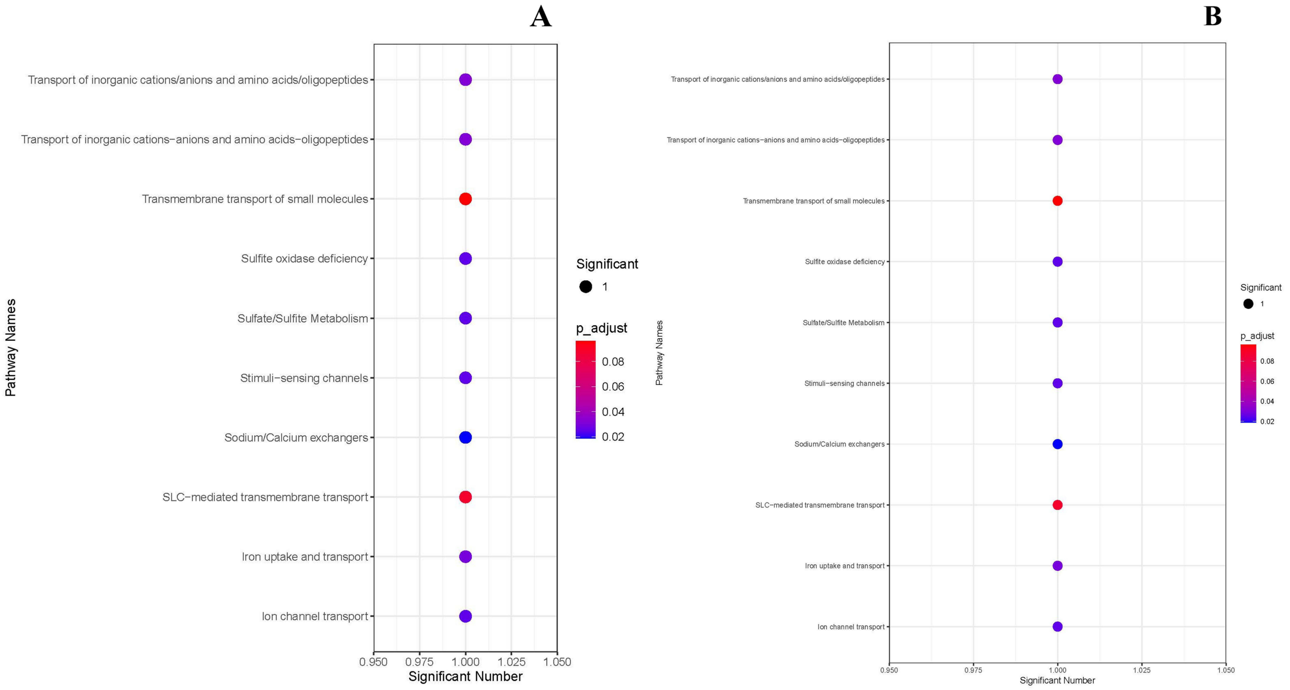

**Figure 6** Enrichment of Metabolic Pathways Involving Metallome elements Associated with CKD. (**A**) Enrichment of metabolic pathways related to metallome elements implicated in CKD occurrence. (**B**) Enrichment of metabolic pathways related to metallome elements implicated in CKD development.

**Table 7** Metabolite Pathways of Metallome Elements Corresponding to the Development of CKD

| Pathway Name | Pathsource | Component Ratio | Background Ratio | *P* | *P*_ adjust | Matched Element | Element ID |
|---|---|---|---|---|---|---|---|
| **CKD Onset** | | | | | | | |
| Metabolism | Reactome | 2/2 | 1265/4289 | 0.087 | 0.094 | Co/ Pb | C00175/C06696 |
| ABC transporters | KEGG | 1/2 | 128/4289 | 0.059 | 0.069 | Co | C00175 |
| Visual phototransduction | Reactome | 1/2 | 62/4289 | 0.029 | 0.037 | Co | C00175 |
| The citric acid (TCA) cycle and respiratory electron transport | Reactome | 1/2 | 54/4289 | 0.025 | 0.036 | Co | C00175 |
| Pyruvate metabolism and Citric Acid (TCA) cycle | Reactome | 1/2 | 42/4289 | 0.019 | 0.034 | Co | C00175 |
| Metabolism of porphyrins | Wikipathways | 1/2 | 37/4289 | 0.017 | 0.034 | Pb | C06696 |
| Heme biosynthesis | Reactome | 1/2 | 28/4289 | 0.013 | 0.034 | Pb | C06696 |
| The phototransduction cascade | Reactome | 1/2 | 21/4289 | 0.010 | 0.034 | Co | C00175 |
| Inactivation, recovery and regulation of the phototransduction cascade | Reactome | 1/2 | 18/4289 | 0.008 | 0.034 | Co | C00175 |
| Interconversion of 2-oxoglutarate and 2-hydroxyglutarate | Reactome | 1/2 | 11/4289 | 0.005 | 0.034 | Co | C00175 |
| **CKD Development** | | | | | | | |
| Transmembrane transport of small molecules | Reactome | 1/2 | 212/4289 | 0.096 | 0.096 | Li | C15473 |
| SLC-mediated transmembrane transport | Reactome | 1/2 | 173/4289 | 0.079 | 0.088 | Li | C15473 |
| Transport of inorganic cations/anions and amino acids/oligopeptides | Reactome | 1/2 | 55/4289 | 0.025 | 0.032 | Li | C15473 |
| Iron uptake and transport | Wikipathways | 1/2 | 38/4289 | 0.018 | 0.029 | Li | C15473 |
| Ion channel transport | Reactome | 1/2 | 27/4289 | 0.013 | 0.025 | Li | C15473 |
| Sulfate/Sulfite Metabolism | SMPDB | 1/2 | 22/4289 | 0.010 | 0.025 | Mo | C00150 |
| Stimuli-sensing channels | Reactome | 1/2 | 13/4289 | 0.006 | 0.025 | Li | C15473 |
| Sodium/Calcium exchangers | Reactome | 1/2 | 4/4289 | 0.002 | 0.019 | Li | C15473 |

**Notes**: Element ID, the element number in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

## Discussion

CKD is a multifactorial disease with a complex and not yet fully understood pathogenesis. In addition to well-established risk factors like diabetes and hypertension, environmental chemicals, including metallome elements, are also significant contributors to CKD risk.[17] It has long been recognized that disorders in Zn and Cu metabolism, resulting from various diseases, can alter kidney structure and function, and that CKD patients exhibit imbalances in essential trace elements such as Fe, Zn, Se, Cu, iodine, and Mn.[18] Lu et al[16] found a positive correlation between elevated urinary Co levels and an increased risk of kidney stones in the American population, suggesting that metallome element changes may elevate the risk of CKD or accelerate its progression. However, most existing studies have focused on a limited number of elements, typically analyzing the impact of individual or a small group of trace elements (eg, Fe, Cu, Zn, Se)[18,19] or toxic metals (eg, Pb, As, Cd, Hg)[20–22] in CKD, with little emphasis on comprehensive metabolic profiling. Liu et al[23] assessed the relationship between plasma metal element concentrations and renal function decline in middle-aged and elderly Chinese individuals, revealing significant correlations between the plasma levels of elements such as Al, Pb, Mo, Rb, and V and declined renal function. These data suggest that metal exposure contributes to an elevated risk of renal impairment. Similarly, other studies have reported that elevated levels of heavy metals in the general population are linked to reduced eGFR,[24] with multiple metal elements exerting synergistic effects that collectively contribute to kidney damage.[25] Liang et al[26] identified associations between Cd, Pb, Hg, Mn, and Se and CKD in a study of adult American CKD patients, proposing that these five metals may act synergistically in the disease's progression. Furthermore, Wang et al[27] observed that metal mixtures were associated with both renal function decline and increased CKD risk, with Pb and Cd emerging as the primary contributors. An increase of one unit in their concentrations corresponded to a 1.60- and 1.41-fold rise in the odds ratio for CKD, respectively. Numerous studies have established that abnormal accumulation or deficiency of metallome elements can disrupt kidney metabolism and function, contributing to the onset of kidney disease and aggravating renal damage in affected individuals.[28–30] Concurrent exposure to multiple metal elements can exacerbate renal injury due to synergistic interactions between these elements. To further investigate the potential impact of metallome elements on CKD pathogenesis and progression, this study employed ICP-MS to quantify the levels of 26 metallome elements in the serum of CKD patients. These included macroelements, essential trace elements, potentially essential trace elements, and potentially toxic metals, with an analysis of their correlations to renal function markers. The results indicated that, compared to the HC group, 13 of the 26 elements were upregulated in the CKD group (comprising 2 macroelements, 3 essential trace elements, 3 potentially essential trace elements, 3 potentially toxic elements, and 4 other metals), while 3 elements were downregulated (including the essential trace element Co, the potentially toxic metal Hg, and the radioactive element U). The alterations in Li, Mn, Ni, Mo, and Pb observed in this study align with findings by Azevedo R et al[31] in hemodialysis patients, while changes in Cu, Zn, and Se differ. Previous studies indicate that eGFR in maintenance hemodialysis patients often falls between 5–8 mL/min/1.73m²,[32] heightening the risk of trace element imbalances in this population.[9,33] The CKD patients included in this study spanned stages G1-G5, suggesting that variations in metallome element levels may result from differences in the pathological conditions across patient populations.

ICP-MS technology was employed to detect and analyze 26 metal elements in the study subjects, revealing distinct patterns of element involvement in CKD initiation and progression. CKD onset was linked to Al, V, Co, Ga, Cs, and Pb, while its progression was associated with Li, V, Mo, and Cs. It is reliable that the analysis of the data took into account the collinearity from interactions between various elements, which ruled out Mg and Ca as risks for CKD occurrence and progression. Previous studies have indicated that during CKD development, metal elements primarily impair renal function by directly damaging renal cells, inducing oxidative stress, and modulating aerobic metabolism,[34–36] contributing to disease onset. In the progressive phase of CKD, the toxic effects of these elements worsen renal injury by disrupting intracellular signaling and influencing substance transport mechanisms,[37–39] thereby accelerating disease progression. The metabolic pathway analysis conducted in this study further corroborates these findings. Previous work has established that environmental contaminants migrate through the soil-plant system into the food chain, where they bioaccumulate and ultimately reach the human body.[40] This process poses significant health risks, including chronic toxicity and potential carcinogenic effects, particularly for populations reliant on locally sourced food from contaminated areas. Additionally, occupational exposures typically involve much higher concentrations of toxic elements than environmental exposures and represent a major risk factor for heavy metal overload in affected workers.[41] These factors may collectively contribute to individual differences.

Lead (Pb) exposure impairs renal function, even at low concentrations, with heightened toxicity in CKD.[42] This study found a significant positive correlation between high serum Pb levels and both Creat and CysC, known CKD risk factors. This association may stem from impaired renal clearance in CKD patients, resulting in Pb accumulation and worsening of renal damage.[43] Furthermore, interactions between Pb and other nephrotoxic elements, such as Cd, can markedly increase the risk of CKD. Co-exposure to Pb and heavy metals has been shown to significantly increase CKD risk.[44] These mechanisms collectively contribute to the deterioration of renal function.

Aluminum (Al), a non-essential mineral, is commonly encountered in daily life, resulting in frequent exposure to the human body. Previous research has indicated that Al accumulation in CKD patients may be linked to bone tissue deposition.[45] In this study, serum Al levels in CKD patients were elevated, with a significant positive correlation observed between Al and Urea, Creat, and CysC. Despite improvements in dialysis water quality and restrictions on Al-containing medications, some dialysis patients continue to exhibit elevated Al levels.[46] Higher serum Al concentrations are strongly associated with reduced eGFR and an increased UACR, with even low Al exposure aggravating renal dysfunction.[47] This highlights the potential underestimation of Al exposure, particularly in CKD patients. Monitoring Al levels in CKD patients is therefore crucial for both the diagnosis and management of the disease.

Cobalt (Co) is an essential trace element and a key component of multiple enzymes, critical to various metabolic processes. Valko et al[48] demonstrated that both V and Co can mediate redox reactions within cells. This study further confirmed Co's protective role in the onset of CKD, as reduced serum Co levels in CKD patients indicate a loss of its protective effect on renal function. In an acute ischemic tubulointerstitial injury model, Co treatment was shown to improve renal function.[49] Co ions in $CoCl2$ have been shown to activate hypoxia-inducible factors in renal cells,[50] slowing GFR decline, reducing albuminuria, and thereby mitigating the progression of renal disease. Furthermore, contrast agents are known to induce renal tubular ischemia and hypoxia, but $CoCl2$ can protect renal tubules and reduce contrast-induced renal damage.[51] These observations collectively highlight the protective effect of Co on renal function.

The kidney serves as the primary organ for the storage and excretion of Mo. Additionally, Mo regulates the proliferation, differentiation, and apoptosis of renal cells, contributing to the preservation of renal structure and function.[52] Dalong et al[53] reported that Mo-based nanoclusters exhibited antioxidant properties and could effectively alleviate clinical symptoms of acute renal injury in mice. However, excessive Mo accumulation can lead to organ toxicity, particularly in the kidneys. This study identified a significant association between elevated serum Mo levels and the biomarkers Urea, Creat, UA, and CysC in patients with CKD, suggesting a potential role of Mo in renal damage and dysfunction. Wu et al[54] observed that Mo exposure increased the number of mitochondria, autophagosomes, and vacuolar mitochondria in renal tissue, disrupting the energy metabolism of renal cells. Bai et al[55] and Cui et al[56] further identified that Mo induced mitochondrial autophagy and dysfunction in renal tubular epithelial cells via the PINK6/Parkin pathway and the CaMKKβ/AMPK/mTOR pathway, with potential synergistic effects. These studies highlight the relationship between Mo and renal dysfunction in CKD patients, but they lack a focus on different stages of CKD. In this study, the analysis of metal elements across various CKD stages revealed that Mo served as an independent risk factor for CKD progression, with better predictive value for disease progression. Excessive Mo exposure can induce oxidative stress and DNA damage, impairing renal cell function.[57] Additionally, Mo disrupts intracellular signaling pathways, contributing to cell dysfunction.[58] Furthermore, the progressive decline in renal function in CKD patients impairs Mo excretion, leading to its accumulation and aggravating its toxic effects on the kidneys.

Lithium (Li) is a trace element with unproven essentiality but known neurological impacts. Its carbonate salt is a primary anti-mania treatment. While it may aid cognition, prolonged or high-dose use carries risks of neurotoxicity and kidney damage.[59,60] Georgin et al[61] reported that even low doses of Li, within the therapeutic range, could cause dilation of cortical tubules in rat kidneys. This study observed that Li levels increased with advancing CKD stages and exhibited a nonlinear dose-response relationship with eGFR. Similarly, Mikkel et al[62] confirmed an association between cumulative Li dosage and CKD risk.

Cesium (Cs) exists as $Cs^+$ ions in organisms. Due to its similarity to potassium (K), it can mimic $K^+$ activity and is absorbed through potassium transport pathways.[63,64] Once introduced into the body, Cs is not readily excreted, and its accumulation to elevated levels can induce nephrotoxicity. This study revealed that Cs levels in CKD patients were significantly higher than those in the HC group, and Cs was identified as an independent risk factor for CKD onset and progression. Akanuma et al[65] demonstrated that $Mg^{2+}$ could mitigate $Cs^+$-induced cellular damage by stabilizing ribosomal structures, thereby enhancing cellular tolerance to $Cs^+$. Additionally, studies have shown that Cs exposure during early pregnancy negatively correlates with GFR, suggesting that excessive Cs exposure may impair renal function in pregnant women.[66]

Vanadium (V), a transition metal element, is mainly ingested through food and is stored in bones and circulates in body as vanadate. Vanadate serves as a substrate for certain enzymes and inhibitors protein tyrosine phosphatases, thereby exerting insulin-like effects, which underscores its role as an essential trace element for the human body. Studies have demonstrated that vanadate or V-containing complexes possess anti-diabetic, anti-tumor, anti-viral, and anti-parasitic properties.[67–73] Despite these therapeutic effects, research on the toxicity of V and its potential applications in CKD diagnosis and treatment remains limited. Taidinda et al[74] observed that low-dose of V enhanced motor development and other functions in mice, while high-dose caused kidney damage. This study also identified a nonlinear dose-response relationship between V and eGFR levels, suggesting its involvement in CKD onset and progression. Wang et al[30] observed a significantly negatively correlated between V and rapid renal function decline in patients with type 2 diabetes. Manuel et al[75] demonstrated that V triggers reactive oxygen species production, directly damaging renal cells and worsening oxidative stress and inflammatory, thus contributing to CKD pathogenesis and progression.

Gallium (Ga) is a trace element with both therapeutic and toxicological roles, particularly in the context of CKD. Its primary medical use is in radionuclide imaging (eg, Ga-67 for nephritis, while Ga-68 for infection). It also possesses inherent antibacterial properties.[76–79] Recent studies highlight Ga's dual role in kidney health, emphasizing its therapeutic benefits while acknowledging its nephrotoxic effects at elevated concentrations. This study observed elevated serum Ga level in CKD patients, which was positively correlated with Urea and an independent risk factor for CKD. However, the precise biological mechanisms underlying Ga's effects remain incompletely understood. Some studies suggest that Ga may bind to transferrin in the bloodstream in a manner similar to Fe,[80] facilitating its transport throughout the body. Ga accumulation can induce nephrotoxicity by disrupting intracellular Ca balance and aggravating oxidative stress responses in kidney cells.[77]

To investigate the impact of metallome elements associated with CKD onset and progression on kidney function, a metabolic pathway analysis was conducted. Among the elements analyzed, it is noteworthy that only Pb and Co had a direct impact on the metabolic pathways associated with aerobic metabolism, thereby contributing to the development of CKD. In contrast, Li and Mo facilitated the progression of CKD by modulating substance transport mechanisms. The results suggest that metal elements implicated in kidney damage are not always directly involved in metabolic processes but may exert indirect effects on renal function. Furthermore, metallome elements participating in substance metabolism do not necessarily induce kidney damage: the kidney may not be the primary target organ, with potential effects extending to other tissues or organs.

Metal elements, particularly certain heavy metals, are well-documented for their potential to induce renal damage and/or exacerbate the progression of kidney disease.[29,81–83] This study investigated the spectrum of metal elements present in the blood of patients with CKD and identified a significant elevation in the levels of various metal elements in these patients. These findings may offer a novel approach for the clinical management of CKD in the future. Specifically, metal chelation therapy could be employed to remove elements present at elevated concentrations that contribute to the onset and progression of kidney disease, particularly Al, Li, Co, Mo, V, Cs, and Pb, thereby preventing the occurrence or delaying the progression of CKD. Additionally, risk assessment tools could be developed to identify populations at high risk for CKD, facilitating early clinical intervention. Furthermore, dietary interventions could be implemented to supplement elements that have a protective effect on renal function, such as Co and low concentrations of V, through food sources and/or specific nutritional supplements, thereby safeguarding the kidneys from damage. Furthermore, the analysis of metabolic pathways involving these metal elements can provide insights into the pathological mechanisms underlying the onset and progression of CKD.

## Limitations

This study is subject to several limitations. Firstly, there is an imbalance in the sample size estimation between the healthy control group and the CKD group. Given the multifactorial etiology of CKD, which includes common conditions such as hypertension, diabetes, and immune factors, we intend to stratify the CKD group based on etiology to investigate the relationship between CKD and the occurrence and progression of metal group elements. Secondly, potential confounding factors, including diet influences (such as pharmaceuticals and nutritional supplements), environmental variables (encompassing regional variations), and occupational exposures, were not considered in this study. It is important to recognize that individual metal exposure can manifest in various ways, and identifying its sources is crucial. Future research will focus on increasing observations in this area to enhance our understanding of the causes and progression of CKD. Thirdly, this study is limited to a single observation of the subjects' blood levels, with a brief research period that restricts the analysis to a cross-sectional framework. Future research will aim to explore the relationship between metal group elements and the progression of CKD through longitudinal observations and disease tracking. Additionally, it is important to note that the detection limit of the ICP-MS instrument employed is 0.001μg/L. Consequently, when sample detection results are below 0.001μg/L, the data are statistically processed as equal to 0.001μg/L. Despite this statistical adjustment, the interpretation of the results remains unaffected, as metal element concentrations below 0.001μg/L are of negligible clinical significance.

## Conclusions

This case-control study investigates the metabolic profiles of CKD patients. While 19 metallome elements, including both macroelements and essential trace elements, exhibit abnormal serum levels in CKD patients, only Al, V, Co, Ga, Cs, and Pb are identified as independent factors influencing the onset of CKD. Additionally, Li, V, Mo, and Cs are found to be independent risk factors for CKD progression. Regular monitoring of the concentrations of specific elements, such as V, Pb and Mo in this study cohort, in the serum of high-risk populations within the region, may facilitate the early diagnosis of CKD induced by these metal elements and assist in tracking the progression of confirmed CKD. The concurrent presence of multiple metal elements appears to have a synergistic effect, exacerbating renal damage in CKD patients. Although Ga and V are often overlooked in clinical practice, they play a direct role in the onset and progression of CKD. Of note, metal element levels are influenced by environmental factors, with regional variations in exposure leading to distinct metabolic profiles. Thus, understanding these metabolic profiles may be valuable for disease diagnosis, treatment, and maintaining overall health.

## Abbreviations

CKD, Chronic Kidney Disease; Creat, Creatinine; UA, Uric Acid; CysC, Cystatin C; C1q, Complement Component 1q; Ca, Calcium; Mg, Magnesium; Cu, Copper; Zn, Zinc; Fe, Ferrum; Mn, Manganese; Se, Selenium; Pb, Lead; Cd, Cadmium; Al, Aluminium; Cr, Chromium; Ge, Germanium; Mo, Molybdenum; Co, Cobalt; V, Vanadium; Sn, Stannum; Ni, Nickel; As, Arsenic; Li, Lithium; Hg, Hydrargyrum; U, Uranium; Ga, Gallium; Rb, Rubidium; Ag, Argentum; Cs, Cesium; Au, Aurum; GFR, Glomerular Filtration Rate; ESKD, End-stage Kidney Disease; eGFR, estimated Glomerular Filtration Rate.

## Data Sharing Statement

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

All experiments were approved by the Ethics Committee of Mianyang Central Hospital (No. P2020030). This study adheres to the ethical principles outlined in the Declaration of Helsinki.

## Acknowledgments

We express our gratitude to IAAST (www.iaast.cn) for providing linguistic assistance during the preparation of this manuscript.

## Funding

This research was supported by Science and Technology Department of Sichuan Province (2019YJ0701 and 2021YJ0239) and NHC Key Laboratory of Nuclear Technology Medical Transformation (Mianyang Central Hospital) (2021HYX005).

## Disclosure

The authors declare no conflicts of interest in this work.

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