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Association of the uric acid-to-HDL cholesterol ratio with cardiorenal syndrome: a two-stage study with external validation and exploratory pathway analysis

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Abstract

Background

Cardiorenal syndrome (CRS) is characterized by the coexistence of cardiac and renal dysfunction and is associated with adverse clinical outcomes. The uric acid-to-high-density lipoprotein cholesterol ratio (UHR) has emerged as a composite metabolic marker with potential links to inflammation and cardiovascular–renal dysfunction; however, its association with CRS remains insufficiently characterized.

Methods

We conducted a two-stage study consisting of a discovery analysis using NHANES (2011–2018) and an external validation analysis using a clinical dataset of 23,090 adults from the Affiliated Lihuili Hospital of Ningbo University. Multivariable logistic regression and restricted cubic spline analyses were used to evaluate the association and possible non-linearity between UHR and CRS. ROC and decision curve analyses were performed as supplementary assessments of discrimination and potential clinical usefulness. Subgroup analyses were conducted to examine consistency across clinical characteristics. To explore possible pathways linking UHR with CRS, we additionally evaluated inflammation-related indices, including the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), using mediation-based exploratory analyses.

Results

Among 9,793 participants in NHANES, 332 participants had CRS. In the fully adjusted model, higher UHR was associated with higher odds of CRS (OR = 1.140, 95% CI: 1.103–1.178, $P < 0.001$). A non-linear association was observed in restricted cubic spline analysis (P for nonlinearity = 0.003). In the external validation cohort, which included 23,090 participants and 971 CRS cases, the association remained statistically significant (OR = 1.04, 95% CI: 1.03–1.04, $P < 0.001$), with evidence of non-linearity as well (P for nonlinearity < 0.001). The association was generally consistent across subgroup analyses, although a significant interaction by sex was observed in the external validation cohort. ROC and decision curve analyses provided supplementary evidence of modest incremental discrimination and net benefit. In exploratory pathway analyses, NLR showed a small but statistically significant mediating signal, whereas PLR showed an inverse signal and SII was not consistently significant across cohorts.

Conclusions

Higher UHR was associated with a greater prevalence of CRS in both a nationally representative US cohort and an external hospital-based cohort. These findings suggest that UHR may reflect underlying metabolic-inflammatory disturbances associated with CRS, with NLR-related inflammatory activation representing a potential intermediary pathway. Prospective studies are needed to clarify temporality, causal mechanisms, and its potential role in clinical risk assessment.

Introduction

CRS is a clinical syndrome characterized by acute or chronic dysfunction of either the heart or kidneys that leads to functional impairment of the other organ[1]. According to the Global Burden of Disease Study, approximately 788 million people worldwide were affected by chronic kidney disease (CKD) in 2023 and impaired kidney function is responsible for 11.5% of all mortality resulting from cardiovascular disease[2]. Even more strikingly, the cardiovascular hazards triggered by CKD frequently outweigh the risks of renal progression itself. Indeed, over 50% of patients with CKD develop cardiovascular complications, which serve as the primary driver of shortened life expectancy[3]. CRS is not only a significant complication of CKD but also the leading cause of death in this population, posing a substantial burden on global healthcare systems and socioeconomic resources[4].

The pathogenesis of CRS is complex, involving interactions among multiple pathophysiological processes, including hemodynamic disturbances (e.g., decreased cardiac output and renal venous congestion), overactivation of neuroendocrine systems (e.g., the renin-angiotensin-aldosterone system [RAAS] and sympathetic nervous system), inflammatory responses, and oxidative stress. Among these, inflammation plays a central role[5]. Currently, systemic immune-inflammatory index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are widely used biomarkers for assessing systemic inflammatory status[6]. They provide efficient and sensitive measures of subclinical inflammation in various diseases[7,8].

The uric acid to high-density lipoprotein cholesterol ratio (UHR) is a novel inflammatory and metabolic biomarker, calculated as the ratio of serum uric acid to high-density lipoprotein cholesterol (HDL-C)[9]. HDL-C exerts anti-inflammatory and antioxidant effects[10] and is closely associated with insulin resistance and metabolic syndrome[11,12]. In contrast, uric acid acts as both an antioxidant and a pro-oxidant; at elevated concentrations, it promotes inflammation and oxidative stress, thereby contributing to cardiac and renal injury[13,14]. Elevated UHR levels have been linked to an increased risk of metabolic syndrome, abdominal aortic aneurysm, non-alcoholic fatty liver disease, and cardiovascular diseases (CVD)[15–18].

Current management of CRS primarily involves personalized comprehensive care, focusing on volume control (e.g., using diuretics or ultrafiltration)[11,12,19–21] and neurohormonal blockade (e.g., RAAS inhibitors and sodium-glucose cotransporter-2 inhibitors [SGLT2])[22–26]. However, due to the lack of specific clinical manifestations and targeted therapies for CRS, early identification of modifiable risk factors is essential for effective intervention[27]. The UHR, derived from routine biochemical tests, is a cost-effective, readily available, and reproducible indicator with high clinical utility. Nevertheless, evidence regarding the association between UHR and CRS remains limited, particularly concerning the potential mediating role of inflammation. Therefore, investigating the relationship between UHR and CRS, as well as the mediating effect of inflammation, is of great significance for early risk stratification and intervention.

This study adopted a two-stage design to evaluate the association, characterize potential non-linear patterns, and explore the clinical relevance of UHR in CRS. First, we utilized data from the National Health and Nutrition Examination Survey (NHANES) 2011–2018 as a discovery cohort to establish the association between UHR and CRS. Subsequently, we conducted external validation on a large-scale, real-world clinical dataset (N = 23,090) from Affiliated Lihuili Hospital of Ningbo University to confirm the robustness and generalizability of our findings. This study aims to: (1) examine the independent association and characterize the potential non-linear dose-response relationship between UHR and CRS using restricted cubic splines (RCS); (2) assess the discriminative ability and clinical net benefit of the UHR-based model via ROC curves and DCA; (3) analyze the mediating role of inflammatory responses (NLR, PLR, and SII) through 1000 bootstrap simulations. By integrating public database discovery with large-scale clinical validation, this research provides a stronger empirical foundation for using UHR in early risk stratification and intervention for CRS.

Methods

Data Source

The present study employed a two-stage design, utilizing both a national public database and an independent clinical validation cohort.

First, the discovery cohort was derived by combining four NHANES cycles (2011–2018). NHANES is a cross-sectional survey designed to assess the health and nutritional status of the non-institutionalized U.S. population through household interviews and standardized physical examinations. All NHANES participants provided informed consent, and the study protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. NHANES uses a complex, multistage probability sampling design to obtain a representative sample of the US population. All analyses incorporated sampling weights, strata, and primary sampling units in accordance with NHANES analytic guidelines.

Second, an external validation cohort was established using real-world clinical data from Affiliated Lihuili Hospital of Ningbo University. This cohort included 23,090 adult participants who underwent routine health examinations between 2015 and 2017. This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the participating hospital.

Study Population

In the discovery phase, we first included data from four NHANES cycles (2011–2018), totaling 39,156 participants. After excluding individuals under 20 years of age (n = 16,539), individuals lacking serum creatinine or cardiovascular disease data required for diagnosing CRS and estimating glomerular filtration rate (eGFR) (n = 2,336), individuals lacking uric acid or high-density lipoprotein cholesterol (HDL-

C) data required for calculating UHR (n = 15), and individuals with missing or zero sampling weights (n = 10,473), 9,793 eligible participants were ultimately included.

In the external validation phase, we retrospectively included 24,572 patients admitted to Affiliated Lihuili Hospital of Ningbo University from 2015 to 2017. To maintain consistency with the discovery cohort, we used the same inclusion and exclusion criteria. After excluding individuals under 20 years of age (n = 960), individuals lacking serum creatinine data required for estimating glomerular filtration rate (eGFR) (n = 271), individuals lacking uric acid or high-density lipoprotein cholesterol (HDL-C) data required for calculating UHR (n = 183), and individuals lacking cardiovascular disease data for determining CRS (n = 68), a total of 23,090 patients were selected.

The detailed screening process for the two cohorts is shown in Fig. 1.

Diagnosis of CRS

The outcome variable, CRS, was defined as the co-presence of CVD and CKD[28]. The ascertainment of these components differed slightly between the two cohorts to accommodate their respective data structures.

For the discovery cohort (NHANES), CVD was defined as a self-reported history of coronary heart disease, angina, congestive heart failure, heart attack, or stroke, determined via standardized questionnaire items: "Has a doctor or other health professional ever told you that you had heart disease/angina/congestive heart failure/heart attack/stroke?".

For the external validation cohort, CVD was ascertained based on clinical diagnosis codes and medical records from the hospital information system, including coronary heart disease, angina, congestive heart failure, myocardial infarction, or stroke.

In both cohorts, CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m². The eGFR was calculated using the CKD-EPI Creatinine Eq. (2009) based on standardized serum creatinine measurements[29].

Participants meeting both CVD and CKD criteria were diagnosed with CRS.

Measurement of UHR

Measurement of UHR. The primary exposure variable was the Uric Acid to HDL-C Ratio (UHR), calculated as UHR (%) = [serum uric acid (mg/dL) / HDL-C (mg/dL)] × 100[16]. In the discovery cohort (NHANES), blood samples were collected by trained professionals at the Mobile Examination Center (MEC) in accordance with standardized protocols. Serum specimens were processed, stored, and shipped to collaborative laboratory services for analysis. Uric acid was measured using the timed endpoint

method[30], and HDL-C concentration was determined using the enzymatic method. Detailed laboratory procedures are available on the NHANES website. In the external validation cohort (Affiliated Lihuili Hospital of Ningbo University), fasting venous blood samples were collected from participants within 24 hours of admission. Serum uric acid and HDL-C levels were measured using standard automated biochemical analyzers in the hospital's central laboratory, in accordance with internal quality-control standards. Notably, to ensure consistency with the NHANES dataset, laboratory values recorded in SI units were converted to mg/dL prior to UHR calculation (conversion factors: 1 mg/dL = 59.48 μmol/L for uric acid; 1 mg/dL = 0.0259 mmol/L for HDL-C).

Measurement of Systemic Inflammation Markers (SII, PLR, NLR)

For the discovery cohort (NHANES), blood specimens were processed using Beckman Coulter counting and classification methods, incorporating Volume, Conductivity, and Scatter (VCS) technology for white blood cell differentiation. Hemoglobin was determined using a single-beam photometer. The detailed laboratory procedures are publicly available on the NHANES website.

For the external validation cohort, systemic inflammation markers were measured using standard automated hematology analyzers at our clinical laboratory. All measurements were conducted by trained professionals in accordance with standardized hospital protocols to ensure data accuracy and reproducibility.

In both cohorts, the inflammatory indices were calculated using identical formulas: SII was calculated as SII = (Platelet count × neutrophil count) / Lymphocyte count[6,31]. PLR = Platelet count / Lymphocyte count, NLR = Absolute neutrophil count / Absolute lymphocyte count[8].

Supplementary machine learning analyses.

In order to further examine the incremental relevance of UHR across different modeling frameworks, supplementary machine learning analyses were performed alongside the primary regression-based analyses. Three models were evaluated, including logistic regression, LASSO logistic regression, and extreme gradient boosting (XGBoost). Two feature sets were compared: a base feature set including established covariates (age, sex/gender, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglycerides, LDL-C, total bilirubin, SII, NLR, and PLR), and an extended feature set with additional inclusion of UHR. Categorical predictors were encoded before model fitting. Models were developed in the discovery cohort and evaluated in the independent hospital-based cohort; internal cross-validation was used during model development, whereas the final supplementary presentation focused on external validation performance. Model performance was assessed primarily using the area under the receiver operating characteristic curve (AUC) and Brier score, and calibration was additionally evaluated for the extended models. SHAP (Shapley additive explanations) analysis was performed in XGBoost to assess global variable importance and the UHR-specific contribution pattern. These

analyses were intended as supplementary model-based assessments and were not designed to establish predictive superiority.

Covariates

Covariates were selected based on established clinical strategies and previous literature regarding risk factors for CRS[32]. In both the discovery and validation cohorts, the following variables were consistently adjusted in the multivariable models:

Demographic data: age, gender, and education level. In the NHANES cohort, race was considered to ensure national representativeness. Meanwhile, in the cohort at Affiliated Lihuili Hospital of Ningbo University, race was not considered because all selected patients were of East Asian descent.

Lifestyle factors: smoking status and alcohol use history, determined through standardized questionnaires or medical history records. Clinical and laboratory indicators: body mass index (BMI), triglycerides (TG), LDL-C, total bilirubin (TBIL), and history of comorbidities, including hypertension and diabetes.

BMI was calculated as weight (kg) / height² (m^2) and categorized as normal weight (< 25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥ 30 kg/m^2)[33].

Statistical Analysis

Statistical analyses were conducted separately for the discovery and validation cohorts to accommodate their distinct sampling designs. For the discovery cohort (NHANES), analyses followed the NHANES analytical guidelines using recommended sampling weights, strata, and clusters to ensure national representativeness. For the validation cohort (local clinical data), standard unweighted descriptive statistics were reported. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. Non-normally distributed data were expressed as median with interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were presented as proportions and compared using the chi-square test. The primary analyses were conducted on eligible participants with complete data for the variables included in each model. To evaluate the robustness of the findings to missingness, sensitivity analyses were additionally performed using multiple imputation by chained equations (MICE, m = 5), and pooled estimates were combined according to Rubin's rules. Multivariable logistic regression was employed to evaluate the association between UHR and CRS. Three hierarchical models were constructed: Model 1 was unadjusted; Model 2 adjusted for age, gender, BMI, education level, smoking, alcohol use, and race (specifically included only in the NHANES cohort analysis); Model 3 further adjusted for clinical comorbidities (hypertension, diabetes) and laboratory indicators (TG, LDL-C, TBIL, SII, PLR, NLR). Restricted cubic spline (RCS) regression was used to explore potential non-linear relationships. Causal mediation analysis was performed using the R package "mediation" with 1000 bootstrap samples to examine whether systemic inflammation indicators (NLR, PLR, and SII) mediated the association between UHR and CRS. The direct effect (DE), indirect effect (IE),

and the proportion mediated (IE/Total Effect) were calculated. Subgroup analyses and interaction tests were performed to ensure consistency across different clinical characteristics. All analyses were performed using R (version 4.0.0) and SPSS (version 25.0). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

In the discovery cohort (NHANES, Table 1A), 9,793 adult participants were included, of whom 332 were diagnosed with CRS, yielding a weighted prevalence of 3.39%. The age of the CRS group was significantly higher than that of the non-CRS group (median age: 76.00 years vs. 47.00 years, $P < 0.001$). Compared with non-CRS patients, CRS patients had a significantly higher comorbidity burden, including hypertension (83.66%), diabetes (38.67%), and a history of smoking (58.31%) (all $P < 0.05$). Metabolically, the CRS group was characterized by high triglycerides and low-density lipoprotein cholesterol (LDL-C) (all $P < 0.05$). Notably, the prevalence of CRS increased across UHR quartiles, rising from the lowest to the highest quartile. Consistent with these findings, the external validation cohort (Table 1B) included 23,090 participants, of whom 971 (4.2%) were diagnosed with CRS. Consistent with the discovery cohort, CRS patients were significantly older than non-CRS patients (median age: 76.00 years vs. 56.00 years, $P < 0.001$) and had a higher prevalence of hypertension and diabetes. Laboratory analyses showed similar metabolic disorders in both groups, with higher UHR levels in the CRS group. Crucially, the validation cohort exhibited more pronounced inflammatory features compared to the discovery cohort: systemic inflammatory markers, including the systemic immune inflammatory index (SII), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), were significantly higher in CRS patients than in the non-CRS group (all $P < 0.001$).

Association between UHR and CRS

Multivariable logistic regression was used to examine the association between UHR and CRS in both the discovery and external validation cohorts. In the discovery cohort (NHANES, Table 2A), higher UHR was associated with higher odds of CRS. In the unadjusted model (Model 1), each 1% increase in UHR was associated with 11.3% higher odds of CRS (OR = 1.113, 95% CI: 1.085–1.141, $P < 0.001$). This association remained statistically significant after adjustment for demographic and lifestyle factors in Model 2 (OR = 1.146, 95% CI: 1.116–1.177, $P < 0.001$) and after further adjustment in Model 3 (OR = 1.140, 95% CI: 1.103–1.178, $P < 0.001$). When UHR was analyzed by quartiles, higher quartiles were also associated with higher odds of CRS. Compared with the lowest quartile (Q1), participants in the highest quartile (Q4) had higher odds of CRS in the fully adjusted model (OR = 7.367, 95% CI: 3.921–13.844, $P < 0.001$), with a significant trend across quartiles (P for trend < 0.001). Similar findings were observed in the external validation cohort (Affiliated Lihuili Hospital of Ningbo University, Table 2B). In the fully adjusted model (Model 3), each 1% increase in UHR was associated with higher odds of CRS (OR = 1.04, 95% CI: 1.03–1.04, $P < 0.001$). Likewise, participants in the highest UHR quartile (Q4) had higher odds of CRS than

those in the lowest quartile (Q1) (OR = 8.12, 95% CI: 5.86–11.25, *P* < 0.001), with a significant trend across quartiles (*P* for trend < 0.001). Overall, UHR showed a consistent positive association with CRS when analyzed as either a continuous or categorical variable in both cohorts.

Sensitivity Analysis

To address potential bias arising from missing data, sensitivity analyses were performed for both the primary and external validation cohorts. Following multiple imputation, multivariable logistic regression analyses were re-conducted. The results for the primary cohort remained consistent with the initial findings (Supplementary Material 1, Table S1). Similarly, the external validation using hospital data yielded robust results across the imputed datasets (Supplementary Material 1, Table S2), further confirming the reliability and generalizability of the association between UHR and CRS.

Mediating Role of Systemic Inflammation Markers (SII, PLR, NLR) in the UHR-CRS Association

Subsequently, parallel mediation analyses were conducted in the discovery and external validation cohorts to explore whether inflammation-related indices (SII, NLR, and PLR) might partly account for the observed association between UHR and CRS. In the discovery cohort (NHANES, Fig. 2A), all three markers showed statistically significant indirect effects. Among them, NLR showed the largest positive indirect effect (IE = 0.0000281, 95% CI: 0.0000131 to 0.0000481, *P* < 0.001), accounting for 2.87% of the total effect. SII also showed a positive indirect effect (IE = 0.0000103, 95% CI: 0.0000005 to 0.0000218, *P* = 0.036), accounting for 1.04% of the total effect. In contrast, PLR showed a negative indirect effect (IE = -0.0000325, 95% CI: -0.0000585 to -0.0000062, *P* = 0.016), corresponding to -3.25% of the total effect. In the external validation cohort (Fig. 2B), NLR again showed a positive indirect effect (IE = 0.000009, 95% CI: 0.000004 to 0.000018, *P* < 0.001), accounting for 1.13% of the total effect. PLR also showed a negative indirect effect (IE = -0.000003, 95% CI: -0.000008 to -0.000001, *P* = 0.024), whereas the indirect effect of SII was not statistically significant (IE = 0.000001, 95% CI: -0.000001 to 0.000004, *P* = 0.480). Overall, these findings provide preliminary support for the involvement of inflammation-related pathways, particularly those reflected by NLR, in the association between UHR and CRS, although the underlying mechanisms warrant further investigation.

Subgroup Analysis and Interaction Test

To further examine whether the association between UHR and CRS differed across population subgroups, subgroup analyses and interaction tests were conducted according to sex, BMI, smoking status, and alcohol use in both the discovery and external validation cohorts. In the discovery cohort, as shown in Table 3A and Fig. 3A, the association between UHR and CRS was generally similar across most subgroups. Statistically significant associations were observed among participants with obesity (OR = 1.164, 95% CI: 1.075–1.259, *P* < 0.001), smokers (OR = 1.119, 95% CI: 1.045–1.197, *P* = 0.002), and non-drinkers (OR = 1.123, 95% CI: 1.022–1.234, *P* = 0.017). However, no significant interactions were identified across sex, BMI, smoking status, or alcohol use (all *P* for interaction > 0.05). In the external

validation cohort, as shown in Table 3B and Fig. 3B, the association between UHR and CRS was also observed across most subgroups. A significant interaction by sex was identified (*P* for interaction < 0.001), with a stronger association in females (OR = 1.064, 95% CI: 1.053–1.074) than in males (OR = 1.030, 95% CI: 1.024–1.037). No significant interactions were found for BMI (*P* = 0.106), smoking status (*P* = 0.510), or alcohol use (*P* = 0.776). Overall, these findings suggest that the positive association between UHR and CRS was generally consistent across subgroups, although possible sex-related heterogeneity was observed in the external validation cohort.

Analysis of Non-linear Relationship between UHR and CRS

Restricted cubic spline (RCS) analyses were performed in both the discovery and external validation cohorts to examine the potential non-linear association between UHR and CRS. The results are presented in Fig. 4A and Fig. 4B. After adjustment for covariates, evidence of a non-linear association between UHR and CRS was observed in both cohorts (NHANES: *P* for nonlinearity = 0.003; Affiliated Lihuili Hospital of Ningbo University: *P* for nonlinearity < 0.001).

Analysis of the Discriminative Ability of UHR for CRS

ROC curve analyses were performed to assess the ability of UHR to discriminate CRS in the two cohorts. In the discovery cohort (NHANES), the area under the curve (AUC) for UHR was 0.682 (95% CI: 0.649–0.714) (Fig. 5A), indicating modest discriminative ability. In the external validation cohort (Affiliated Lihuili Hospital of Ningbo University), the AUC was 0.766 (95% CI: 0.750–0.781) (Fig. 5B). These findings indicate that UHR showed measurable discriminative performance in both cohorts, with a higher AUC observed in the external validation cohort.

Decision Curve Analysis of Adding UHR to the Base Model

Decision curve analysis (DCA) was performed to examine the potential incremental value of adding UHR to a model containing established covariates. Two models were compared: a base model including age, sex, race (NHANES only), education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglycerides, LDL-C, total bilirubin, SII, NLR, and PLR, and a second model with additional inclusion of UHR. In the discovery cohort (NHANES), the model including UHR showed a slightly higher net benefit than the base model over a threshold probability range of 1.0% to 54.0%, with a maximum net benefit difference of 0.0029 (Fig. 6A). Similar findings were observed in the external validation cohort (Affiliated Lihuili Hospital of Ningbo University), where the model including UHR showed a modest net benefit increase over a threshold range of 0.3% to 57.1%, with a maximum difference of 0.0038 (Fig. 6B). The magnitude of net benefit was modest across both cohorts, suggesting that the incremental clinical utility of UHR beyond established risk factors may be limited.

Supplementary machine learning model comparison

Supplementary machine learning analyses were performed to further examine the relevance of UHR across different modeling frameworks. In external validation, the results were model-dependent. The addition of UHR was associated with a higher AUC in XGBoost (0.896 vs. 0.914), whereas no improvement was observed in logistic regression (0.850 vs. 0.800) or LASSO logistic regression (0.851 vs. 0.809). The decrease in performance observed in regression-based models after inclusion of UHR may reflect collinearity or shared information with existing covariates rather than absence of relevance. Overall, these findings suggest that the incremental contribution of UHR may be model-dependent and should be interpreted as supplementary evidence rather than consistent predictive improvement. Detailed performance metrics are provided in Supplementary Table S3, and the corresponding external ROC curves are shown in Supplementary Figure S1.

Variable importance of UHR across models

In SHAP-based variable importance analysis of XGBoost, UHR ranked as the second most important predictor after age and showed greater relative importance than several conventional clinical variables, including hypertension, NLR, total bilirubin, SII, and LDL. This finding suggests that UHR contributed meaningful model information beyond established covariates. Detailed SHAP-based importance rankings are provided in Supplementary Table S4, and the corresponding SHAP importance plot is shown in Supplementary Figure S2.

Model interpretation of UHR using SHAP

SHAP dependence analysis in XGBoost indicated that the contribution of UHR to model-predicted CRS probability was non-linear. Specifically, the SHAP value of UHR was slightly negative or near zero at lower levels and increased progressively at higher UHR levels. This pattern was broadly consistent with the non-linear association observed in the restricted cubic spline analyses. The corresponding UHR-specific dependence pattern is shown in Supplementary Figure S3.

Discussion

In this two-stage cross-sectional study, we observed a consistent positive association between UHR and CRS in both a nationally representative US cohort and an external hospital-based Chinese cohort. This association remained statistically significant after adjustment for potential confounding factors in both datasets. Sensitivity analyses yielded similar results, and subgroup analyses suggested that the association was generally consistent across most strata, although sex-related heterogeneity was observed in the external validation cohort. In addition, exploratory analyses of inflammation-related indices suggested that metabolic-inflammatory pathways, particularly those reflected by NLR, may partly contribute to the observed association. Restricted cubic spline analyses further suggested a non-linear association between UHR and CRS. ROC and decision curve analyses provided additional supportive evidence regarding the discriminative performance and incremental value of UHR, but these findings should not be considered the primary basis for interpretation. Overall, our findings suggest that UHR is a readily available metabolic marker associated with CRS across two distinct study settings.

The biological plausibility of the UHR-CRS association stems from an imbalance between pro-oxidant/pro-inflammatory factors and antioxidant/anti-inflammatory systems[18,34]. Elevated uric acid directly triggers oxidative stress and activates the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines such as IL-1β, which induces endothelial dysfunction and RAAS overactivation—pathways that collectively damage cardiac and renal tissues[13,14]. Simultaneously, the reduction or dysfunction of HDL-C—a key protective factor involved in reverse cholesterol transport and antioxidant defense—further impairs the body's buffering capacity against this systemic damage[35]. When UHR is elevated, it not only indicates an increase in the "damaging factor" uric acid[36,37], but also often accompanies a decrease in or dysfunction of the "protective factor" HDL-C, leading to a significant reduction in the body's buffering capacity against oxidative stress and inflammatory responses[38,39], thereby potentially contributing to cardiac and renal injury. Our exploratory mediation analyses suggested that inflammation-related indices, particularly NLR, may partly contribute to the observed association. Beyond inflammation, the metabolic syndrome pathway likely plays a synergistic role; insulin resistance associated with high UHR promotes sodium retention and renal fibrosis[40–42]. As a composite indicator, UHR captures metabolic abnormality information, as represented by both uric acid and HDL-C, potentially reflecting the metabolic basis of cardiorenal comorbidity better than single indicators[18,34]. Additionally, abnormal lipid metabolism is another potential mechanism: reduced HDL-C levels impair its ability to clear lipids from tissues via reverse cholesterol transport[43], leading to lipid deposition in nephrons and consequent decline in renal function[44], while renal impairment can further exacerbate uric acid retention, forming a vicious cycle[45].

The non-linear pattern observed in the restricted cubic spline analyses suggests that the association between UHR and CRS may be more complex than a simple linear relationship. Although this finding may indicate that both higher and lower ranges of UHR deserve attention, the cross-sectional design precludes inference about an optimal target range or therapeutic threshold. This observation should therefore be interpreted cautiously and requires confirmation in prospective studies.

Supplementary machine learning analyses provided additional model-based information regarding the relevance of UHR. The incremental effect of adding UHR was not consistent across algorithms in external validation. Although XGBoost showed improved external discrimination after inclusion of UHR, this pattern was not observed in logistic regression or LASSO logistic regression, indicating that the incremental predictive value of UHR was model-dependent. SHAP-based interpretation further suggested that UHR retained high relative importance and exhibited a non-linear contribution pattern broadly consistent with the restricted cubic spline analyses. These findings should therefore be interpreted as supplementary model-based evidence of relevance rather than as evidence of uniform predictive superiority.

This study has several strengths. First, the two-stage design, combining discovery in NHANES with external validation in a large hospital-based cohort, enhances the reproducibility and generalizability of the findings. Second, the analyses incorporated multivariable adjustment, subgroup analyses,

assessment of potential non-linearity, and supplementary exploratory modeling. Several limitations should also be acknowledged. First, because of the cross-sectional design, temporal relationships and causality cannot be established. Second, CRS in this study was operationally defined as the co-presence of CVD and CKD, which may not fully capture the pathophysiological spectrum of clinically adjudicated cardiorenal syndrome. In addition, CVD ascertainment differed between cohorts, with self-reported history in NHANES and diagnosis-based ascertainment in the hospital cohort, which may have introduced outcome misclassification. Finally, residual confounding may remain despite extensive adjustment, including unmeasured factors such as genetic background, medication use, and healthcare-related differences. Future prospective and multi-center studies are needed to clarify temporality, underlying mechanisms, and the potential clinical relevance of UHR in CRS assessment.

Conclusion

Higher UHR was associated with a greater prevalence of CRS in both the national discovery cohort and the independent external validation cohort. These findings support the potential relevance of UHR as a readily available metabolic marker associated with CRS. Exploratory analyses further suggested that metabolic-inflammatory pathways, particularly those reflected by NLR, may partly contribute to this association. Future prospective multicenter studies are needed to clarify temporality, underlying mechanisms, and the potential incremental clinical relevance of UHR in CRS assessment.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

KZF: conceived, designed, and wrote the manuscript. WZQ: performed statistical calculations and data interpretation. MHY: conceived and revised the manuscript. CZK: reviewed the revised manuscript.

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Not applicable.

Data availability

Data supporting this study were accessed from the NHANES public repository (www.cdc.gov/nchs/nhanes) and the in-hospital digital platform of Affiliated Lihuili Hospital of Ningbo University.

Ethics approval and consent to participate

For the discovery cohort, because ethical approval and informed consent were previously obtained by the National Center for Health Statistics (NCHS) Research Ethics Review Board for the original NHANES project, this study was exempt from additional informed consent for this dataset. For the external validation cohort, this retrospective study was approved by the Ethics Committee of Affiliated Lihuili Hospital of Ningbo University (Approval No. 2026-112). Given the retrospective nature of the study using anonymized clinical data, the requirement for individual informed consent was also waived by the Ethics Committee of Affiliated Lihuili Hospital of Ningbo University.

Trial registration

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ye, W. Q. W., Qureshi, M. A. & Auguste, B. Cardiorenal syndrome. *Cmaj* 195, E1154 (2023). https://doi.org:10.1503/cmaj.230226
2. Mark, P. B.*et al.* Global, regional, and national burden of chronic kidney disease in adults, 1990–2023,and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. *The Lancet* 406, 2461–2482 (2025). https://doi.org:10.1016/S0140-6736(25)01853-7
3. Li, Y. *et al.* Chronic kidney disease is associated with increased risk of sudden cardiac death. *Nature Communications* 16, 9180 (2025). https://doi.org:10.1038/s41467-025-64254-9
4. Uduman, J. Epidemiology of Cardiorenal Syndrome. *Advances in Chronic Kidney Disease* 25, 391–399 (2018). https://doi.org:https://doi.org/10.1053/j.ackd.2018.08.009
5. Ramírez-Guerrero, G., Ronco, C. & Reis, T. Cardiorenal Syndrome and Inflammation: A Forgotten Frontier Resolved by Sorbents? *Cardiorenal Medicine* 14, 454–458 (2024). https://doi.org:10.1159/000540123
6. Yücel, K. B. *et al.* The relationship between systemic immune inflammation index and survival in patients with metastatic renal cell carcinomatreated withtyrosine kinase inhibitors. *Sci Rep* 12, 16559 (2022). https://doi.org:10.1038/s41598-022-20056-3
7. Chen, C. *et al.* Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Potential Predictors of Prognosis in Acute Ischemic Stroke. *Front Neurol* 11, 525621 (2020). https://doi.org:10.3389/fneur.2020.525621

8. Tamaki, S. *et al.* Combination of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios as a Novel Predictor of Cardiac Death in Patients With Acute Decompensated Heart Failure With Preserved Left Ventricular Ejection Fraction: A Multicenter Study. *J Am Heart Assoc* 12, e026326 (2023). https://doi.org:10.1161/jaha.122.026326
9. Kurtkulagi, O. *et al.* Hashimoto's thyroiditis is associated with elevated serum uric acid to high density lipoprotein-cholesterol ratio. *Romanian Journal of Internal Medicine* 59, 403–408 (2021). https://doi.org:10.2478/rjim-2021-0023
10. Barter, P. J. *et al.* Antiinflammatory properties of HDL. *Circ Res* 95, 764–772 (2004). https://doi.org:10.1161/01.Res.0000146094.59640.13
11. Chen, T. K., Hoenig, M. P., Nitsch, D. & Grams, M. E. Advances in the management of chronic kidney disease. *Bmj* 383, e074216 (2023). https://doi.org:10.1136/bmj-2022-074216
12. Pitt, B. *et al.* Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes. *N Engl J Med* 385, 2252–2263 (2021). https://doi.org:10.1056/NEJMoa2110956
13. Wang, M., Lin, X., Yang, X. & Yang, Y. Research progress on related mechanisms of uric acid activating NLRP3 inflammasome in chronic kidney disease. *Ren Fail* 44, 615–624 (2022). https://doi.org:10.1080/0886022x.2022.2036620
14. Shen, S., He, F., Cheng, C., Xu, B. & Sheng, J. Uric acid aggravates myocardial ischemia-reperfusion injury via ROS/NLRP3 pyroptosis pathway. *Biomed Pharmacother* 133, 110990 (2021). https://doi.org:10.1016/j.biopha.2020.110990
15. Xie, Y. *et al.* Association of serum uric acid-to-high-density lipoprotein cholesterol ratio with non-alcoholic fatty liver disease in American adults: a population-based analysis. *Front Med (Lausanne)* 10, 1164096 (2023). https://doi.org:10.3389/fmed.2023.1164096
16. Xu, J. *et al.* Diagnostic value of uric acid to high-density lipoprotein cholesterol ratio in abdominal aortic aneurysms. *Ann Med* 56, 2357224 (2024). https://doi.org:10.1080/07853890.2024.2357224
17. Ahari, R. K. *et al.* Association of atherosclerosis indices, serum uric acid to high-density lipoprotein cholesterol ratio and triglycerides-glucose index with hypertension: A gender-disaggregated analysis. *J Clin Hypertens (Greenwich)* 26, 645–655 (2024). https://doi.org:10.1111/jch.14829
18. Kocak, M. Z. *et al.* Serum uric acid to HDL-cholesterol ratio is a strong predictor of metabolic syndrome in type 2 diabetes mellitus. *Rev Assoc Med Bras (*1992) 65, 9–15 (2019). https://doi.org:10.1590/1806-9282.65.1.9
19. Novak, J. E. & Ellison, D. H. Diuretics in States of Volume Overload: Core Curriculum 2022. *Am J Kidney Dis* 80, 264–276 (2022). https://doi.org:10.1053/j.ajkd.2021.09.029
20. Mohiuddin, N., Frinak, S. & Yee, J. Sodium-based osmotherapy for hyponatremia in acute decompensated heart failure. *Heart Fail Rev* 27, 379–391 (2022). https://doi.org:10.1007/s10741-021-10124-7
21. Arrigo, M., Cippà, P. E. & Mebazaa, A. Cardiorenal Interactions Revisited: How to Improve Heart Failure Outcomes in Patients With Chronic Kidney Disease. *Curr Heart Fail Rep* 15, 307–314 (2018). https://doi.org:10.1007/s11897-018-0406-8

22. Elenjickal, E. J. *et al.* Efficacy and Safety of Sodium-Glucose Cotransporter-2 Inhibitors in Patients with and without Advanced CKD: Systematic Review and Meta-Analysis. *Clin J Am Soc Nephrol* 20, 788–809 (2025). https://doi.org:10.2215/cjn.0000000693
23. Yamada, T. *et al.* Cardiovascular and renal outcomes with SGLT-2 inhibitors versus GLP-1 receptor agonists in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and network meta-analysis. *Cardiovasc Diabetol* 20, 14 (2021). https://doi.org:10.1186/s12933-020-01197-z
24. Mavrakanas, T. A., Tsoukas, M. A., Brophy, J. M., Sharma, A. & Gariani, K. SGLT-2 inhibitors improve cardiovascular and renal outcomes in patients with CKD: a systematic review and meta-analysis. *Sci Rep* 13, 15922 (2023). https://doi.org:10.1038/s41598-023-42989-z
25. Garcia Sanchez, J. J. *et al.* Treatments for Chronic Kidney Disease: A Systematic Literature Review of Randomized Controlled Trials. *Adv Ther* 39, 193–220 (2022). https://doi.org:10.1007/s12325-021-02006-z
26. Poznyak, A. V. *et al.* Renin-Angiotensin System in Pathogenesis of Atherosclerosis and Treatment of CVD. *Int J Mol Sci* 22 (2021). https://doi.org:10.3390/ijms22136702
27. Savira, F. *et al.* Cardiorenal syndrome: Multi-organ dysfunction involving the heart, kidney and vasculature. *British Journal of Pharmacology* 177, 2906–2922 (2020). https://doi.org:https://doi.org/10.1111/bph.15065
28. Banerjee, S. & Radak, T. Association between food insecurity, cardiorenal syndrome and all-cause mortality among low-income adults. *Nutrition and Health* 25, 245–252 (2019). https://doi.org:10.1177/0260106019869069
29. Levey, A. S. *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150, 604–612 (2009). https://doi.org:10.7326/0003-4819-150-9-200905050-00006
30. Bazmandegan, G. *et al.* Uric acid to HDL ratio: A marker for predicting incidence of metabolic syndrome in patients with type II diabetes. *Nutr Metab Cardiovasc Dis* 34, 1014–1020 (2024). https://doi.org:10.1016/j.numecd.2023.12.022
31. Geraghty, J. R. *et al.* Systemic Immune-Inflammation Index Predicts Delayed Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage. *Neurosurgery* 89, 1071–1079 (2021). https://doi.org:10.1093/neuros/nyab354
32. Zhang, P., Mo, D., Zeng, W. & Dai, H. Association between triglyceride-glucose related indices and all-cause and cardiovascular mortality among the population with cardiovascular-kidney-metabolic syndrome stage 0–3: a cohort study. *Cardiovasc Diabetol* 24, 92 (2025). https://doi.org:10.1186/s12933-025-02642-7
33. Weir, C. B. & Jan, A. in *StatPearls* (StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC., 2025).
34. Yazdi, F. *et al.* Investigating the relationship between serum uric acid to high-density lipoprotein ratio and metabolic syndrome. *Endocrinol Diabetes Metab* 5, e00311 (2022). https://doi.org:10.1002/edm2.311

35. Holzer, M. *et al.* Dialysis Modalities and HDL Composition and Function. *J Am Soc Nephrol* 26, 2267–2276 (2015). https://doi.org:10.1681/asn.2014030309
36. Richette, P. & Bardin, T. Gout. *The Lancet* 375, 318–328 (2010). https://doi.org:10.1016/S0140-6736(09)60883-7
37. Hu, A. M. & Brown, J. N. Comparative effect of allopurinol and febuxostat on long-term renal outcomes in patients with hyperuricemia and chronic kidney disease: a systematic review. *Clin Rheumatol* 39, 3287–3294 (2020). https://doi.org:10.1007/s10067-020-05079-3
38. Kochan, Z., Szupryczynska, N., Malgorzewicz, S. & Karbowska, J. Dietary Lipids and Dyslipidemia in Chronic Kidney Disease. *Nutrients* 13 (2021). https://doi.org:10.3390/nu13093138
39. von Eckardstein, A., Nordestgaard, B. G., Remaley, A. T. & Catapano, A. L. High-density lipoprotein revisited: biological functions and clinical relevance. *Eur Heart J* 44, 1394–1407 (2023). https://doi.org:10.1093/eurheartj/ehac605
40. Jia, G., Lockette, W. & Sowers, J. R. Mineralocorticoid receptors in the pathogenesis of insulin resistance and related disorders: from basic studies to clinical disease. *Am J Physiol Regul Integr Comp Physiol* 320, R276-r286 (2021). https://doi.org:10.1152/ajpregu.00280.2020
41. Nistala, R. & Whaley-Connell, A. Resistance to insulin and kidney disease in the cardiorenal metabolic syndrome; role for angiotensin II. *Mol Cell Endocrinol* 378, 53–58 (2013). https://doi.org:10.1016/j.mce.2013.02.005
42. Jindal, A., Brietzke, S. & Sowers, J. R. Obesity and the Cardiorenal Metabolic Syndrome: Therapeutic Modalities and Their Efficacy in Improving Cardiovascular and Renal Risk Factors. *Cardiorenal Med* 2, 314–327 (2012). https://doi.org:10.1159/000343803
43. Lund, J. *et al.* Human HDL subclasses modulate energy metabolism in skeletal muscle cells. *J Lipid Res* 65, 100481 (2024). https://doi.org:10.1016/j.jlr.2023.100481
44. Luo, Z., Chen, Z., Hu, J. & Ding, G. Interplay of lipid metabolism and inflammation in podocyte injury. *Metabolism - Clinical and Experimental* 150 (2024). https://doi.org:10.1016/j.metabol.2023.155718
45. Petreski, T., Ekart, R., Hojs, R. & Bevc, S. Hyperuricemia, the heart, and the kidneys - to treat or not to treat? *Ren Fail* 42, 978–986 (2020). https://doi.org:10.1080/0886022x.2020.1822185

Tables

Table 1

A. Baseline characteristics of the discovery cohort (NHANES 2011–2018).

A Variables	Total (n = 9,793[1])	CRS		P-value
		No (n = 9,461[1])	Yes (n = 332[1])	
Age, years, median (Q_1, Q_3)	47.00 (33.00, 61.00)	47.00 (33.00, 60.00)	76.00 (68.00, 80.00)	< 0.001
Gender, n (%)				0.200
Male	4,752 (48.24%)	4,586 (48.37%)	166 (50.00%)	
Female	5,041 (51.76%)	4,875 (51.63%)	166 (50.00%)	
Race, n (%)				< 0.001
Mexican American	1,327 (8.75%)	1,304 (8.88%)	23 (3.32%)	
Other Hispanic	1,047 (6.40%)	1,022 (6.48%)	25 (2.85%)	
Non-Hispanic White	3,718 (64.69%)	3,523 (64.43%)	195 (75.70%)	
Non-Hispanic Black	2,085 (11.29%)	2,019 (11.28%)	66 (11.65%)	
Other race/multiracial	1,616 (8.87%)	1,593 (8.93%)	23 (6.48%)	
Education level, n (%)				< 0.001
Less Than 9th Grade	922 (5.14%)	874 (5.01%)	48 (10.35%)	
9-11th Grade	1,279 (9.88%)	1,224 (9.73%)	55 (16.11%)	
High School Grad/GED or Equivalent	2,153 (22.51%)	2,067 (22.41%)	86 (26.69%)	
Some College or AA degree	2,970 (31.80%)	2,881 (31.92%)	89 (26.82%)	
College Graduate or above	2,462 (30.67%)	2,408 (30.92%)	54 (20.04%)	
BMI, kg/m2, n (%)				0.017
Normal weight (< 25)	2,828 (28.82%)	2,759 (28.95%)	69 (23.34%)	
Overweight (25-29.9)	3,123 (32.50%)	3,022 (32.64%)	101 (26.84%)	
Obese (> 30)	3,725 (38.68%)	3,574 (38.41%)	151 (49.81%)	
Triglyceride, mg/dL, median (Q_1, Q_3)	96.00 (65.00, 143.00)	95.00 (65.00, 143.00)	113.00 (81.00, 162.00)	< 0.001
LDL-C, mg/dL, median (Q_1, Q_3)	110.00 (88.00, 134.00)	110.00 (88.00, 135.00)	88.00 (67.00, 119.00)	< 0.001

A Variables	Total (n = 9,793[1])	CRS		P-value
		No (n = 9,461[1])	Yes (n = 332[1])	
Total bilirubin, mg/dL, median (Q_1, Q_3)	0.60 (0.40, 0.80)	0.60 (0.40, 0.80)	0.60 (0.50, 0.80)	0.666
SII, median (Q_1, Q_3)	440.35 (318.18, 624.29)	439.20 (317.09, 620.54)	522.50 (371.65, 712.89)	< 0.001
NLR, median (Q_1, Q_3)	1.94 (1.47, 2.58)	1.93 (1.46, 2.56)	2.62 (1.96, 3.46)	< 0.001
PLR, median (Q_1, Q_3)	119.09 (96.00, 147.22)	119.05 (96.11, 147.06)	120.00 (85.79, 153.08)	0.670
UHR, %, median (Q_1, Q_3)	10.23 (7.45, 13.92)	10.19 (7.39, 13.78)	13.70 (9.68, 18.29)	< 0.001
UHR, %, n (%)				< 0.001
Q1	2,450 (26.05%)	2,419 (26.44%)	31 (9.88%)	
Q2	2,448 (24.25%)	2,390 (24.41%)	58 (17.72%)	
Q3	2,448 (25.04%)	2,369 (24.99%)	79 (27.07%)	
Q4	2,447 (24.66%)	2,283 (24.16%)	164 (45.32%)	
Hypertension, n (%)				< 0.001
Yes	3,686 (33.55%)	3,411 (32.34%)	275 (83.66%)	
No	6,094 (66.45%)	6,038 (67.66%)	56 (16.34%)	
Diabetes, n (%)				< 0.001
Yes	1,392 (10.32%)	1,249 (9.64%)	143 (38.67%)	
No	8,130 (87.32%)	7,955 (88.09%)	175 (55.20%)	
Borderline	266 (2.36%)	252 (2.27%)	14 (6.13%)	
Alcohol use, n (%)				0.021
Yes	1,316 (16.11%)	1,260 (15.92%)	56 (24.61%)	
No	6,369 (83.89%)	6,170 (84.08%)	199 (75.39%)	
Smoking status, n (%)				< 0.001
Yes	4,260 (43.84%)	4,076 (43.49%)	184 (58.31%)	

A Variables	Total (n = 9,793[1])	CRS		P- value
		No (n = 9,461[1])	Yes (n = 332[1])	
No	5,525 (56.16%)	5,377 (56.51%)	148 (41.69%)	

Table 1

B. Baseline characteristics of the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015–2017).

Variables	Total (n = 23,090)	CRS		P-value
		No (n = 22,119)	Yes (n = 971)	
Age, years, median (Q_1, Q_3)	57.00 (45.00, 68.00)	56.00 (44.00, 67.00)	76.00 (66.00, 83.00)	< 0.001
Gender, n (%)				< 0.001
Male	10,598 (45.9%)	10,052 (45.4%)	546 (56.2%)	
Female	12,492 (54.1%)	12,067 (54.6%)	425 (43.8%)	
Education level, n (%)				< 0.001
High school	2,401 (10.40%)	2,340 (10.58%)	61 (6.28%)	
Illiterate	1,814 (7.86%)	1,645 (7.44%)	169 (17.40%)	
Junior college	1,544 (6.69%)	1,516 (6.85%)	28 (2.88%)	
Middle school	6,369 (27.58%)	6,135 (27.74%)	234 (24.10%)	
Primary school	7,789 (33.73%)	7,363 (33.29%)	426 (43.87%)	
Secondary vocational school	727 (3.15%)	708 (3.20%)	19 (1.96%)	
University or above	2,446 (10.59%)	2,412 (10.90%)	34 (3.50%)	
BMI, kg/m2, n (%)				0.010
Normal weight (< 25)	16,932 (73.33%)	16,255 (73.49%)	677 (69.72%)	
Overweight (25-29.9)	5,445 (23.58%)	5,193 (23.48%)	252 (25.95%)	
Obese (> 30)	713 (3.09%)	671 (3.03%)	42 (4.33%)	
Triglyceride, mg/dL, median (Q_1, Q_3)	106.20 (78.76, 149.56)	106.20 (78.76, 149.56)	111.51 (84.08, 154.88)	< 0.001

Notes: Continuous variables with non-normal distribution: median (interquartile range); categorical variables: percentages (%). Between-group comparisons: Mann-Whitney U test for continuous variables; Rao-Scott adjusted chi-square test for categorical variables. All medians and percentages were weighted using NHANES survey weights, while sample sizes (n) reflect unweighted counts. Q1-Q4 were grouped into study participants based on the quartile range of the UHR level.

Abbreviations: UHR: uric acid to high-density lipoprotein cholesterol ratio; CRS: Cardiorenal syndrome; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; SII: Systemic Immune Inflammation Index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Variables	Total (n = 23,090)	CRS		P-value
		No (n = 22,119)	Yes (n = 971)	
LDL-C, mg/dL, median (Q_1, Q_3)	95.73 (75.27, 117.73)	96.50 (76.43, 118.50)	78.74 (58.67, 105.18)	< 0.001
Total bilirubin, mg/dL, median (Q_1, Q_3)	0.70 (0.53, 0.97)	0.57 (0.38, 0.87)	0.71 (0.53, 0.97)	< 0.001
SII, median (Q_1, Q_3)	515.67 (320.86, 932.11)	510.42 (318.94, 917.37)	689.33 (385.71, 1268.29)	< 0.001
NLR, median (Q_1, Q_3)	2.44 (1.60, 4.40)	2.39 (1.58, 4.30)	3.74 (2.29, 7.25)	< 0.001
PLR, median (Q_1, Q_3)	132.93 (100.00, 183.00)	132.50 (100.37, 181.76)	146.86 (99.13, 217.20)	< 0.001
UHR, %, median (Q_1, Q_3)	6.56 (4.73, 9.17)	6.44 (4.66, 8.93)	10.72 (7.58, 15.75)	< 0.001
UHR, %, n (%)				< 0.001
Q1	5,773 (25.0%)	5,721 (25.9%)	52 (5.4%)	
Q2	5,772 (25.0%)	5,670 (25.6%)	102 (10.5%)	
Q3	5,773 (25.0%)	5,547 (25.1%)	226 (23.3%)	
Q4	5,772 (25.0%)	5,181 (23.4%)	591 (60.9%)	
Hypertension, n (%)				< 0.001
Yes	7,149 (30.96%)	6,411 (28.98%)	738 (76.00%)	
No	15,941 (69.04%)	15,708 (71.02%)	233 (24.00%)	
Diabetes, n (%)				< 0.001
Yes	2,554 (11.06%)	2,271 (10.27%)	283 (29.15%)	
No	20,536 (88.94%)	19,848 (89.73%)	688 (70.85%)	
Alcohol use, n (%)				0.108
Yes	3,494 (15.13%)	3,329 (15.05%)	165 (16.99%)	

Notes: Continuous variables with non-normal distribution: median (interquartile range); categorical variables: percentages (%). Between-group comparisons: Mann-Whitney U test for continuous variables; Rao-Scott adjusted chi-square test for categorical variables. All medians and percentages were weighted using NHANES survey weights, while sample sizes (n) reflect unweighted counts. Q1-Q4 were grouped into study participants based on the quartile range of the UHR level.

Abbreviations: UHR: uric acid to high-density lipoprotein cholesterol ratio; CRS: Cardiorenal syndrome; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; SII: Systemic Immune Inflammation Index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Variables	Total (n = 23,090)	CRS		P-value
		No (n = 22,119)	Yes (n = 971)	
No	19,596 (84.87%)	18,790 (84.95%)	806 (83.01%)	
Smoking status, n (%)				0.001
Yes	4,424 (19.16%)	4,199 (18.98%)	225 (23.17%)	
No	18,666 (80.84%)	17,920 (81.02%)	746 (76.83%)	

Notes: Continuous variables with non-normal distribution: median (interquartile range); categorical variables: percentages (%). Between-group comparisons: Mann-Whitney U test for continuous variables; Rao-Scott adjusted chi-square test for categorical variables. All medians and percentages were weighted using NHANES survey weights, while sample sizes (n) reflect unweighted counts. Q1-Q4 were grouped into study participants based on the quartile range of the UHR level.

Abbreviations: UHR: uric acid to high-density lipoprotein cholesterol ratio; CRS: Cardiorenal syndrome; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; SII: Systemic Immune Inflammation Index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Table 2

A. Weighted logistic regression analysis of UHR and CRS in the discovery cohort (NHANES 2011–2018).

	Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
UHR	1.113 (1.085, 1.141)	< 0.001	1.146 (1.116, 1.177)	< 0.001	1.140 (1.103, 1.178)	< 0.001
Categories						
Q 1	Reference	/	Reference	/	Reference	/
Q 2	1.962 (1.098, 3.505)	0.023	2.205 (1.169, 4.157)	0.015	2.198 (1.130, 4.275)	0.02
Q 3	3.033 (1.801, 5.107)	< 0.001	3.813 (2.073, 7.014)	< 0.001	3.595 (1.877, 6.886)	< 0.001
Q 4	5.145 (3.258, 8.125)	< 0.001	8.042 (4.682, 13.812)	< 0.001	7.367 (3.921, 13.844)	< 0.001
P for trend	/	< 0.001	/	< 0.001	/	< 0.001

Model 1: unadjusted; Model 2: adjusted for age, gender, race, education level, smoking status, alcohol use, BMI; Model 3: adjusted for age, gender, race, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR.

Table 2

B. Logistic regression analysis of UHR and CRS of the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015–2017).

	Model 1		Model 2		Model 3	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
UHR	1.04 (1.04, 1.05)	< 0.001	1.04 (1.04, 1.05)	< 0.001	1.04 (1.03, 1.04)	< 0.001
Categories						
Q 1	Reference	/	Reference	/	Reference	/
Q 2	1.98 (1.41, 2.77)	< 0.001	1.83 (1.3, 2.57)	< 0.001	1.87 (1.31, 2.66)	< 0.001
Q 3	4.48 (3.31, 6.07)	< 0.001	3.66 (2.68, 5.01)	< 0.001	3.7 (2.66, 5.14)	< 0.001
Q 4	12.55 (9.43, 16.71)	< 0.001	9.19 (6.81, 12.41)	< 0.001	8.12 (5.86, 11.25)	< 0.001
P for trend	/	< 0.001	/	< 0.001	/	< 0.001

Model 1: unadjusted; Model 2: adjusted for age, gender, education level, smoking status, alcohol use, BMI; Model 3: adjusted for age, gender, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR.

Abbreviations: UHR: uric acid to high-density lipoprotein cholesterol ratio; CRS: Cardiorenal syndrome; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; SII: Systemic Immune Inflammation Index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; OR: odds ratio; CI: confidence interval.

Table 3

A. Subgroup analysis of the association of UHR and CRS in the discovery cohort (NHANES 2011–2018).

Subgroup	OR (95% CI)	P	P for interaction
Gender			0.321
Male	0.998 (0.836, 1.192)	0.981	
Female	1.116 (0.950, 1.311)	0.174	
BMI			0.157
Normal weight	1.032 (0.745, 1.428)	0.847	
Overweight	1.065 (0.889, 1.276)	0.481	
Obese	1.164 (1.075, 1.259)	< 0.001	
Smoking status			0.781
Yes	1.119 (1.045, 1.197)	0.002	
No	1.084 (0.923, 1.272)	0.314	
Alcohol use			0.737
Yes	1.063 (0.900, 1.255)	0.460	
No	1.123 (1.022, 1.234)	0.017	

Table 3

B. Subgroup analysis of the association of UHR and CRS in the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015–2017).

Subgroup	OR (95% CI)	P	P for interaction
Gender			< 0.001
Male	1.03 (1.024, 1.037)	< 0.001	
Female	1.064 (1.053, 1.074)	< 0.001	
BMI			0.106
Normal weight	1.037 (1.031, 1.044)	< 0.001	
Overweight	1.054 (1.03, 1.078)	< 0.001	
Obese	1.043 (0.994, 1.094)	0.0769	
Smoking status			0.51
Yes	1.045 (1.033, 1.058)	< 0.001	
No	1.042 (1.036–1.048)	< 0.001	
Alcohol use			0.776
Yes	1.041 (1.03, 1.053)	< 0.001	
No	1.043 (1.037–1.049)	< 0.001	

Figures

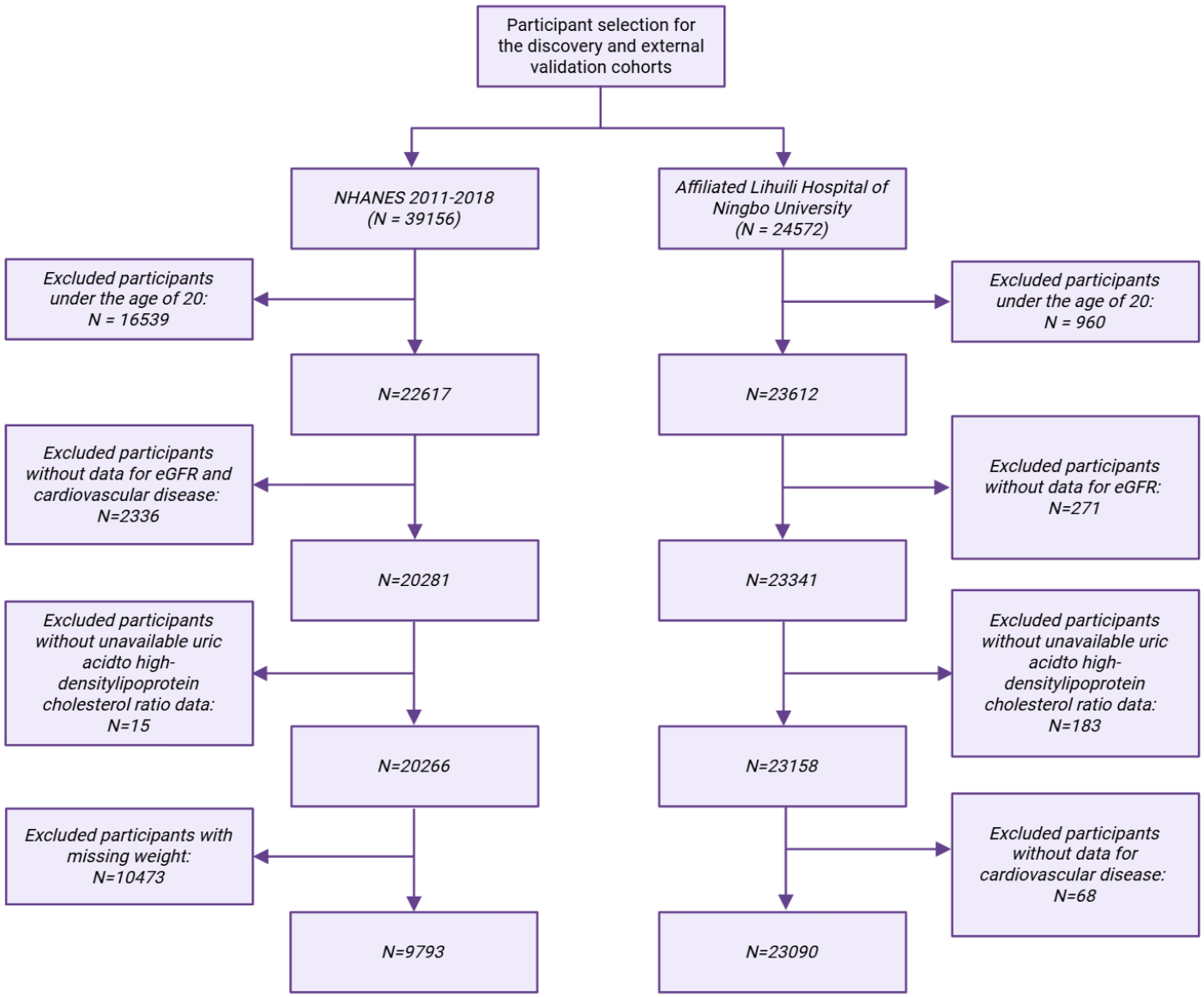


Figure 1

Flowchart of participant selection for the discovery and external validation cohorts.

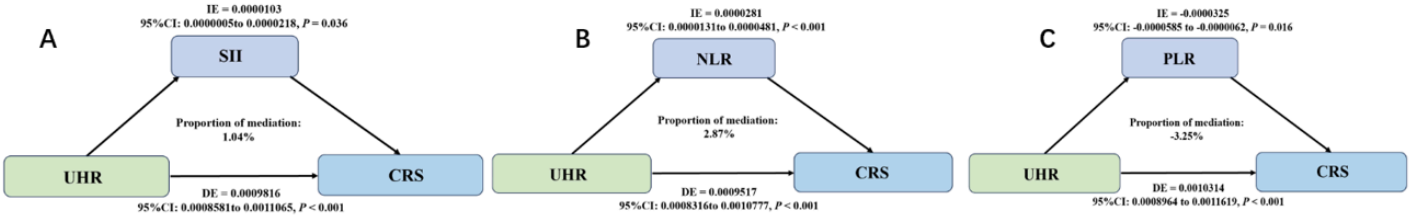


Figure 2A.

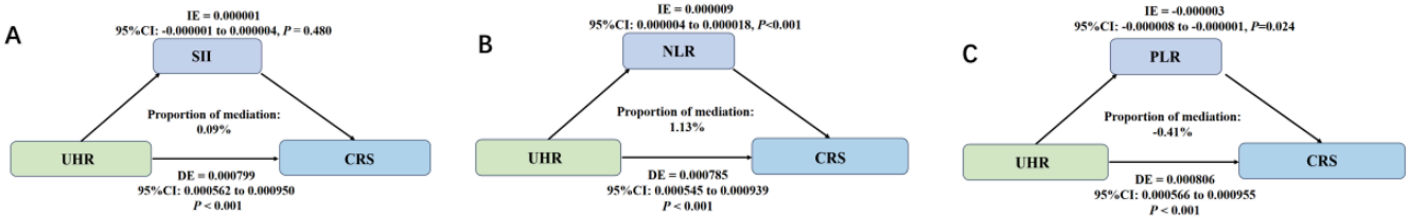


Figure 2B.

Figure 2

2A. Estimated proportion of the association between UHR and CRS mediated by systemic inflammation markers (SII, NLR, and PLR) in the discovery cohort (NHANES 2011–2018). Models were adjusted for age, gender, race, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglycerides, LDL-C, and total bilirubin.

2B. Estimated proportion of the association between UHR and CRS mediated by systemic inflammation markers (SII, NLR, and PLR) in the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015-2017). Models were adjusted for age, gender, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglycerides, LDL-C, and total bilirubin.

Abbreviations: UHR: uric acid to high-density lipoprotein cholesterol ratio; CRS: Cardiorenal syndrome; SII: Systemic Immune Inflammation Index; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; IE: indirect effect; DE: direct effect; CI: confidence interval.

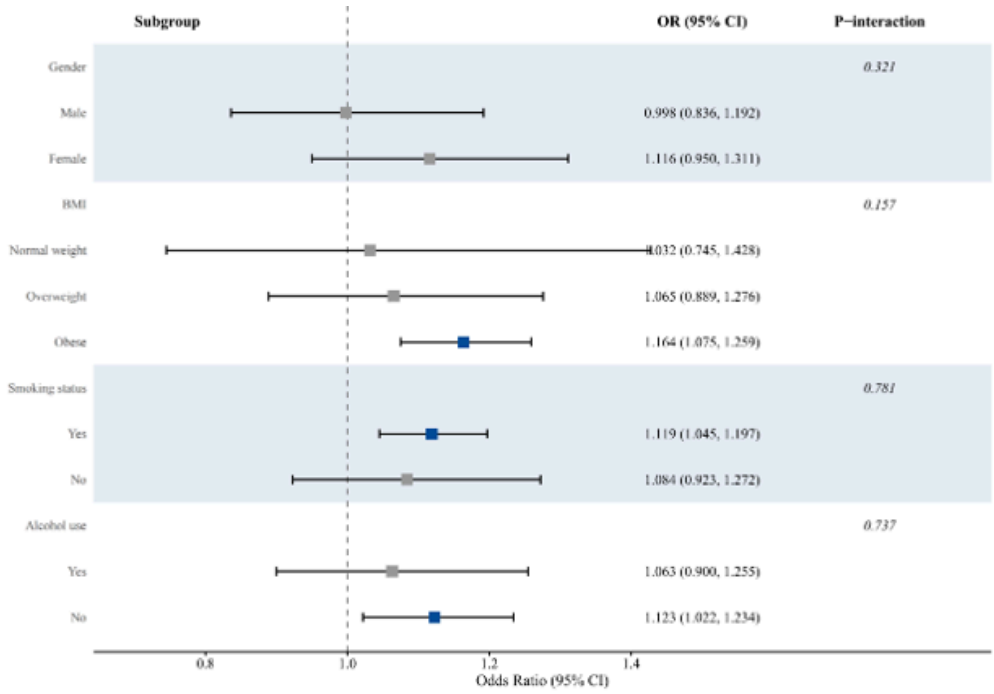


Figure 3A.

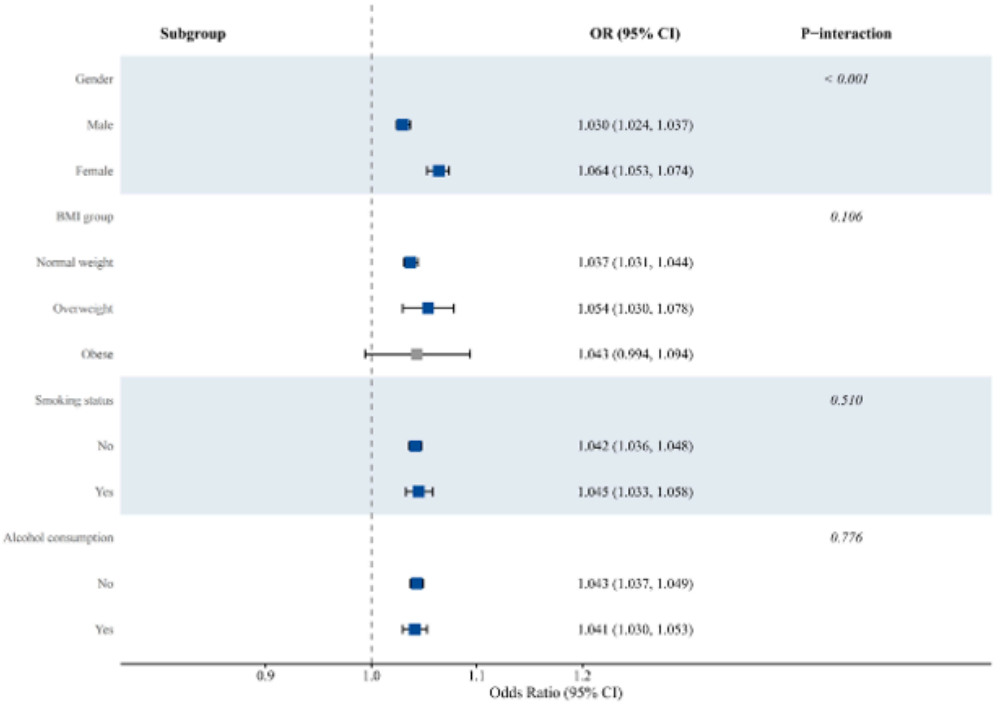


Figure 3B.

Figure 3

3A. Forest plot of subgroup analysis of the association between UHR and CRS in the discovery cohort (NHANES 2011–2018).

3B. Forest plot of subgroup analysis of the association between UHR and CRS in the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015-2017).

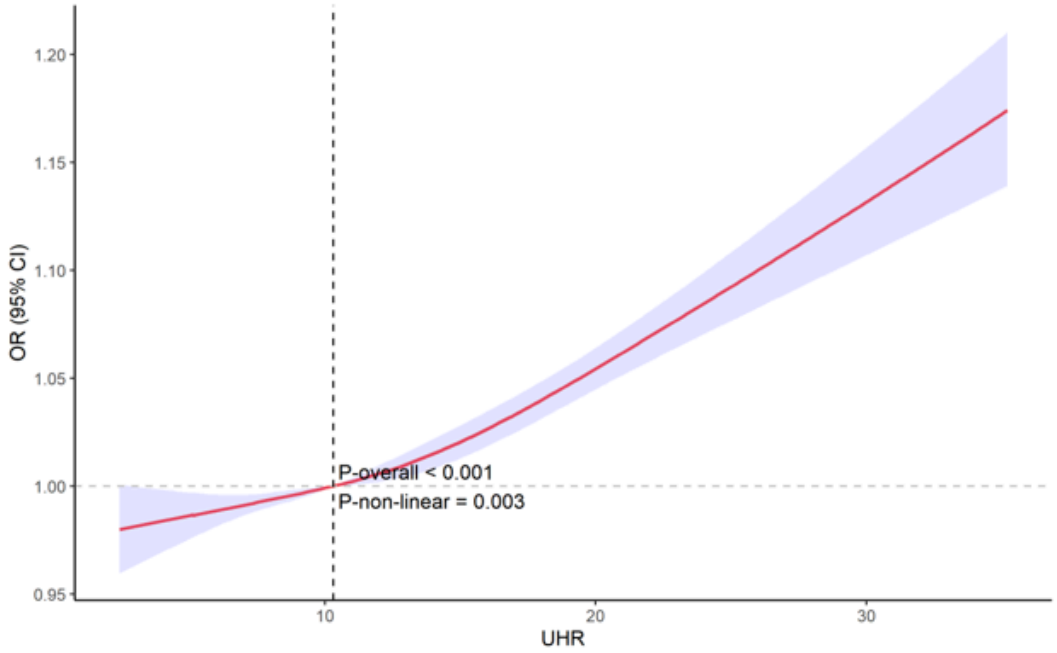


Figure 4A.

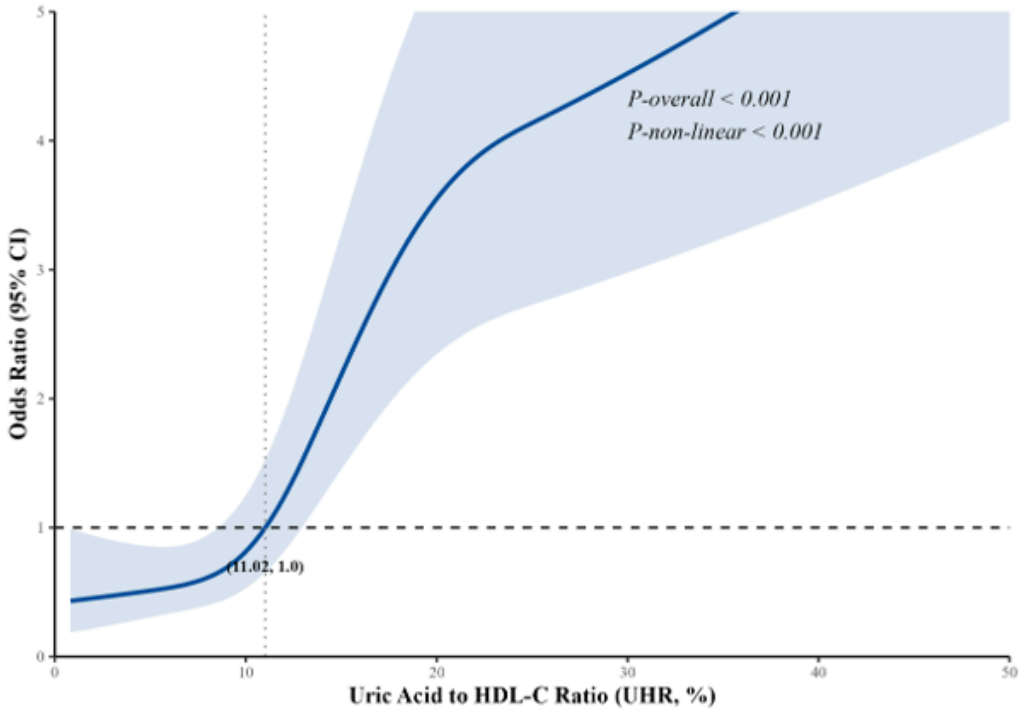


Figure 4B.

Figure 4

4A. Restricted cubic spline explores the potential nonlinear relationships between UHR and CRS in the discovery cohort (NHANES 2011–2018). The 95% confidence levels (shaded areas) were adjusted for age, gender, race, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR.

4B. Restricted cubic spline explores the potential nonlinear relationships between UHR and CRS in the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015-2017). The 95% confidence levels (shaded areas) were adjusted for age, gender, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR.

Abbreviations: UHR: uric acid to high-density lipoprotein cholesterol ratio; OR: odds ratio; CI: confidence interval.

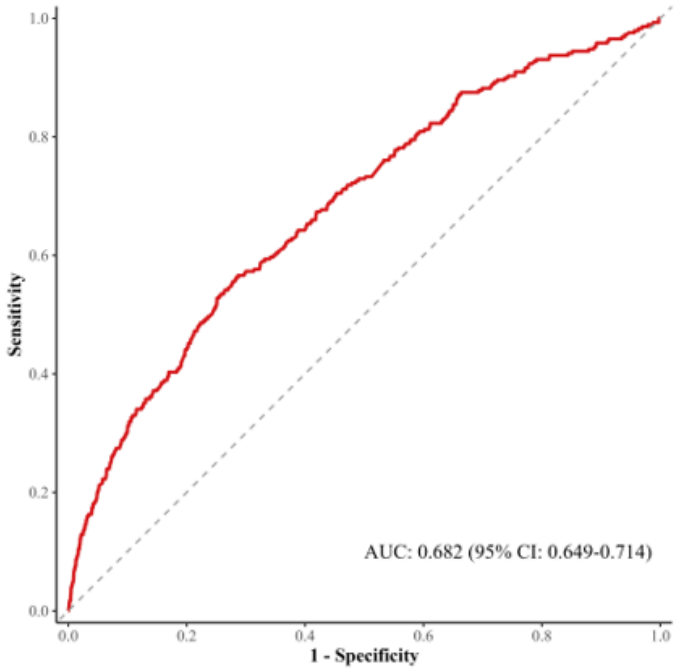


Figure 5A.

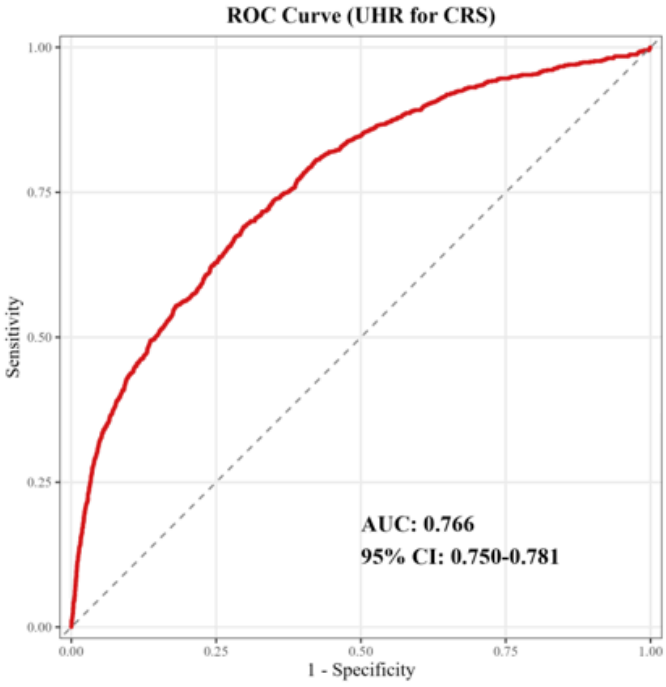
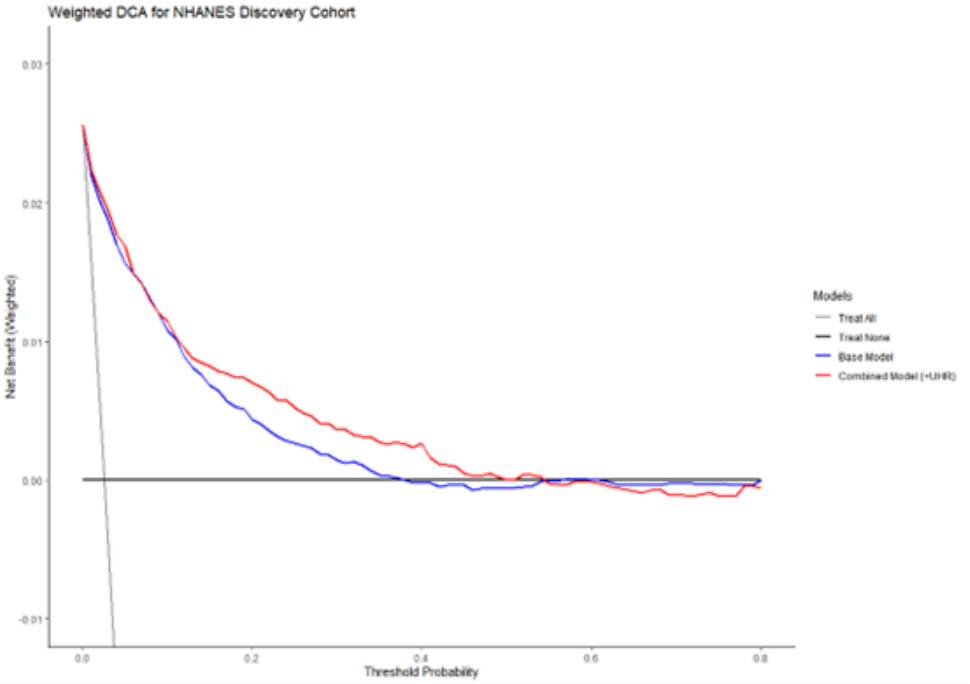


Figure 5B.

Figure 5

5A. ROC curve analysis for evaluating the predictive performance of UHR for CRS in the discovery cohort (NHANES 2011–2018).

5B. ROC curve analysis for evaluating the predictive performance of UHR for CRS in the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015-2017).



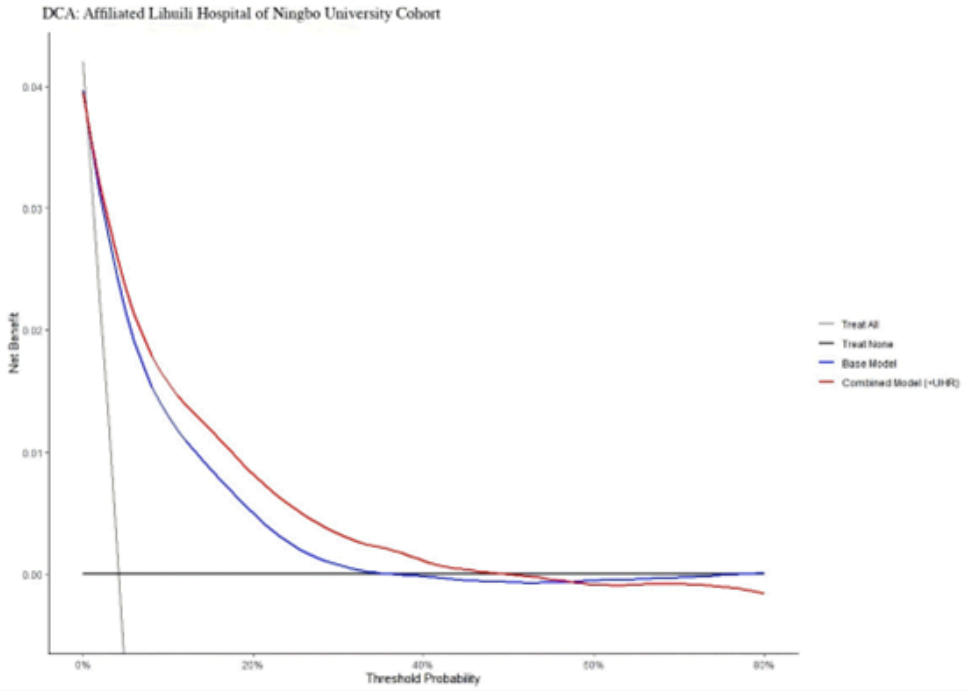


Figure 6

6A. DCA in the discovery cohort (NHANES 2011–2018)

Base Model: Constructed using age, gender, race, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR. Combined(+UHR): Constructed using UHR, age, gender, race, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR. Treat All：The strategy of assuming all patients have CRS and treating/screening everyone. Treat None: The strategy of assuming no patients have CRS and treating/screening no one.

6B. DCA in the external cohort (Affiliated Lihuili Hospital of Ningbo University 2015-2017).

Base Model: Constructed using age, gender, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR. Combined(+UHR): Constructed using UHR, age, gender, education level, smoking status, alcohol use, BMI, hypertension, diabetes, triglyceride, LDL-C, total bilirubin, SII, NLR, PLR. Treat All：The strategy of assuming all patients have CRS and treating/screening everyone. Treat None: The strategy of assuming no patients have CRS and treating/screening no one.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx