Effect of Uric Acid and Hypersensitive C-reactive Protein on Cardiovascular Disease in Patients with Chronic Kidney Disease

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Abstract: Objectives: To explore the effects of uric acid(UA) and hypersensitive C-reactive(hs-CRP) protein on cardiovascular disease in chronic kidney disease. Methods: Using the prospective cohort study method, patients with chronic kidney disease who participated in Kailuan Group's health examination for the first time from 2006 to 2012 were selected as the observation objects, and the new cardiovascular disease was taken as the endpoint event, and the uric acid and hs-CRP levels were grouped, which were as follows: low UA/low hs-CRP group, the high UA/low hs-CRP, low UA/high hs-CRP and high UA/high hs-CRP groups. Multivariate Cox proportional hazards regression was used to analyze the effects of different groups on cardiovascular disease. Result: Cox regression analysis showed that after adjusting for confounding factors such as age and sex, compared with low uric acid and low hs-CRP group, the cardiovascular disease HR (95%CI) of the high uric acid group alone, high hs-CRP group alone, and high uric acid high hs-CRP group were 1.27(1.10-1.46), 1.25(1.14-1.38), and 1.34(1.11-1.61), respectively, all $P < 0.01$. The combined effect between UA and hs-CRP was associated with cardiovascular disease risk (P for interaction < 0.05). Conclusions: Uric acid and hs-CRP had a combined effect on increased risk of CVD in patients with CKD, and the association was independent of patients' baseline eGFR levels.

***Keywords*:** chronic kidney disease population; cardiovascular disease; combined exposure; cohort study

1. Introduction

Chronic Kidney Diseases (CKD) has become a global public health problem, with approximately 690 million people worldwide living with CKD in 2017 [1], placing a huge medical and economic burden on society and healthcare systems. According to the results of the sixth China Chronic Disease and Risk Factor Surveillance, the prevalence of CKD in China is 8.2%, with an estimated 82 million adults suffering from CKD[2]. With the aging of China's population and the increasing incidence of diseases such as diabetes and hypertension year by year, the incidence of CKD also shows a rising trend [3].

Cardiovascular disease (CVD) is a common complication of CKD and the leading cause of death [1]. In addition to controlling traditional cardiovascular risk factors, such as hypertension, diabetes and dyslipidemia, inflammation represented by hs-CRP is also an important risk factor for CVD in patients with CKD [4]. uric acid (UA) is the final product of purine metabolism in the body and is considered another indicator of inflammation in addition to hs-CRP. The prevalence of hyperuricemia in patients with CKD in China ranges from 36.6% to 50.0%[5], and the prevalence increases significantly with the progression of CKD [6]. A meta-analysis by Luo et al confirmed that high UA levels were significantly associated with cardiovascular mortality in patients with CKD [7]. However, UA levels are easily affected by factors such as diet [5,6], and studies have shown that combined exposure to UA and hs-CRP can predict the risk of CVD in the general population significantly better than high UA alone [8]. At present, the relationship between UA and hs-CRP on the occurrence of CVD and subtypes in CKD patients remains unclear. We used the Kailuan study cohort (registration number :ChiCTR-TNRC-11001489) to investigate the effects of uric acid and hypersensitive C-reactive protein levels on the occurrence of cardiovascular disease in chronic kidney disease patients.

2. Objects and methods

2.1 Research object

The Kailuan Study is a large prospective cohort study based on a functional community population. From 2006 to 2007, Kailuan General Hospital and its 11 affiliated hospitals conducted the first health examination and collected relevant data for the current employees and retirees of Kailuan Group, and then conducted a health examination every two years. The physical examination includes uric acid test, hypersensitive C-reactive protein test, urine routine test and kidney function

test. This study was approved by the Ethics Committee of Kailuan General Hospital, and all participants provided written informed consent.

This study included CKD patients who first attended a Kailuan health examination between 2006 and 2012. CKD is defined as eGFR < 60 mL/min/1.73㎡ and/or proteinuria ≥1+ (> 30mg/g) [9]. eGFR was calculated using the formula of the Collaborative Group on Epidemiology of chronic kidney disease [10]. After excluding participants with no uric acid or hypersensitive C-reactive protein data at baseline (n=669), a history of cardiovascular disease (n=1864), and a history of dialysis or kidney transplantation (n=129), a total of 17,708 patients with CKD were included in the final analysis.

2.2 Data and methods

2.2.1 Data Collection

Anthropometric indicators: Height and body mass were measured by calibrated RGZ-120 body mass scale, accurate to 0.1cm height, accurate to 0.1kg body mass, and calculated body mass index (BMI) = body mass (kg)/height (㎡). Blood pressure measurement: The right brachial artery blood pressure is measured by a calibrated table-top mercury sphygmomanometer by uniformly trained and qualified medical personnel.

Laboratory index test: Fasting for more than 8h, fasting venous blood was collected, and all blood samples were analyzed by Hitachi 7600 automatic biochemical analyzer. Biochemical indicators include uric acid, hypersensitive C-reactive protein, creatinine, fasting blood glucose, total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), etc. Serum hs-CRP levels were determined by high sensitivity immunoturbidimetry. Serum uric acid and creatinine levels were determined by oxidase method. Urine test strips were used to detect proteinuria, and the test results were negative, small, 1+, 2+, 3+ and 4+. Urine samples are analyzed at the Dirui N-600 semi-automatic urine analyzer.

Other indicators: smoking, alcohol consumption, education level, history of gout, hypertension, diabetes, and use of antihypertensive, hypoglycemic, and lipid-lowering drugs were collected through a unified standardized questionnaire.

2.2.2 Related Definitions

Hypertension: systolic blood pressure ≥140mmHg (1mmHg= 0.133kPa) and/or diastolic blood pressure ≥90mmHg, or systolic blood pressure < 140mmHg and diastolic blood pressure < 90mmHg but using antihypertensive drugs or history of hypertension [11]. Diabetes: defined as fasting blood glucose > 7.0mmol or using hypoglycemic agents or having a history of diabetes despite fasting blood glucose < 7.0mmol [12]. Smoking: defined as having a history of smoking or currently smoking. Drinking: defined as having a history of drinking or currently drinking alcohol. End-stage renal disease: defined as eGFR < 15 mL/min/1.73㎡[13].

2.2.3 Grouping and follow-up

(1) Male UA level ≥420μmol/L and female UA level ≥360μmol/L were divided into high uric acid group. Male UA level < 420μmol/L and female UA level < 360μmol/L were divided into low uric acid group [14].

(2) According to the clinical significance of hs-CRP, hypersensitive C-reactive protein < 3mg/L was divided into low hs-CRP group, and hypersensitive C-reactive protein ≥3mg/L was divided into high hs-CRP group.

(3) The study subjects were divided into 4 groups :low UA/low hs-CRP group (UA- hs-CRP-); high UA/low hs-CRP group (UA+ hs-CRP-); low UA/high hs-CRP group(UA-hs-CRP+) ; High UA/high CRP group (UA+hs-CRP+).

The time when the first physical examination was completed was the starting point of follow-up, and the occurrence of CVD was the end event. CVD was defined as stroke, myocardial infarction, coronary stent placement, atrial fibrillation, and heart failure. If more than one event occurs, the time and event at which the final event occurs first are the ending points. If no CVD occurred, the last follow-up was December 31, 2021. These events were all confirmed by professional physicians in the inpatient records.

2.2.4 Statistical methods

All data analysis was performed using SAS 9.4. Measurement data conforming to normal distribution were represented by mean ± standard deviation, ANOVA was used for comparison between groups, median (P25, P75) was used for measurement data of skew distribution, non-parametric test (Kruskal-Wallis) was used for comparison between groups, and counting data were represented by frequency and percentage. Inter-group comparison was performed using c2. Kaplan-Meier method was used to calculate the cumulative incidence of cardiovascular diseases and subtypes in different groups, and log-rank test was used to evaluate the differences between groups. Multivariate Cox proportional hazard regression was used to analyze the effect of different groups on the occurrence of cardiovascular disease in the chronic kidney disease population. Cox proportional risk model was constructed to analyze the risk of myocardial infarction, heart failure and stroke. To investigate

whether there were differences in CVD risk among different subgroups.

To further explore the effects of uric acid and hypersensitive C-reactive protein on CVD events, taking into account the potential effects of gender, age, smoking, drinking, and eGFR on CVD, We stratified the included population by sex (male or female), age (≥65 years or < 65 years), smoking (yes or no), drinking (yes or no), and eGFR (≥ 45 or < 45mL/min/1.73 ㎡). In the above analysis, the multiplicative interactions with UA and hs-CRP were analyzed.

3. Results

3.1 General situation of different groups of study population

The mean age of the subjects was (55.5±14.1) years. Among them, 13591 (75.6%) were males. In UA(+)hs-CRP(+) group, the mean age, body mass index, systolic blood pressure, diastolic blood pressure, fasting blood glucose, triglyceride, total cholesterol and low density lipoprotein cholesterol of the subjects were higher, while the high density lipoprotein cholesterol was lower, with statistical significance (P < 0.05). (Table 1)

Table 1. Baseline characteristics of the chronic kidney disease population

Item	Total (n=17708)	UA(-) hs-CRP(-) (n=12597)	UA(+) hs-CRP(-) (n=1204)	UA(-) hs-CRP(+) (n=3290)	UA(+) hs-CRP(+) group(n=617)	P-value
Age (y)	55.5±14.1	54.2±13.5	57.6±14.9	58.8±14.7	60.5±16.4	<0.001
Male (%)	13591(75.6)	9604(76.3)	994(82.6)	2510(76.3)	483(78.2)	<0.001
Smoking (%)	5797(32.7)	3976(31.6)	533(44.2)	1052(31.9)	236(38.2)	<0.001
Drinking (%)	5608(31.7)	3904(30.9)	540(44.8)	934(28.3)	230(37.2)	<0.001
BMI (kg/ ㎡)	25.4±3.5	25.1±3.4	26.2±3.6	25.8±3.7	27.0±4.0	<0.001
SBP(mmHg)	137.2±22.5	135.8±22.1	141.9±22.8	139.8±23.3	142.9±23.3	<0.001
DBP (mmHg)	86.2±12.3	85.7±12.1	88.2±13.2	86.9±12.7	88.3±13.7	<0.001
FBG(mmol/L)	5.7±2.1	5.7±2.0	5.6±1.9	5.8±1.9	6.0±2.5	<0.001
TG (mmol/L)	1.9±1.6	1.9±1.5	2.6±2.4	2.0±1.5	2.6±2.2	<0.001
TC(mmol/L)	4.9±1.3	4.8±1.3	5.2±1.2	4.9±1.3	5.3±1.3	<0.001
LDL-C(mmol/L)	2.6±0.8	2.6±0.7	2.5±0.9	2.6±1.0	2.7±1.0	<0.001
HDL-C(mmol/L)	1.6±0.4	1.6±0.4	1.5±0.4	1.5±0.4	1.4±0.4	<0.001
hs-CRP(mg/L)	1.1(0.4,2.6)	0.7(0.3,1.3)	1.1(0.5,1.7)	5.3(3.7,8.8)	6.0(4.1,9.1)	<0.001
UA(μmol/L)	295.4±91.7	271.9±65.3	478.8±79.2	283.3±66.9	481.0±75.5	<0.001
eGFR(mL/min/1.73 ㎡)	57.8±19.6	57.4±18.8	54.5±20.2	60.8±20.7	57.44±25.4	<0.001
Proteinuria (paper result ≥1+)	3908(22.1)	2407(19.1)	284(23.6)	1023(31.1)	194(31.4)	<0.001
History of gout (number,%)	166(0.9)	85(0.6)	40(3.3)	21(0.3)	20(3.2)	<0.001

Note: Data are expressed as mean ± standard deviation, median (P25, P75), or n (percent).

3.2 Association between different groupings and CVD event risk

During a mean follow-up of (11.24±3.74) years. There were 2725 new CVD events, including 437 myocardial infarction, 748 heart failure, and 1337 stroke. The number of CVD cases in each group was 1751, 229, 616 and 129, respectively. The incidence density of CVD in each group was 12.02/1000 years, 18.11/1000 years, 17.70/1000 years and 21.47/1000 years, respectively, and the cumulative incidence was 14.64%, 22.62%, 21.32% and 25.90%, respectively. The Log-rank test showed that the cumulative incidence of CVD, myocardial infarction, heart failure and stroke were significantly different among different groups (P < 0.05). (Figure 1)

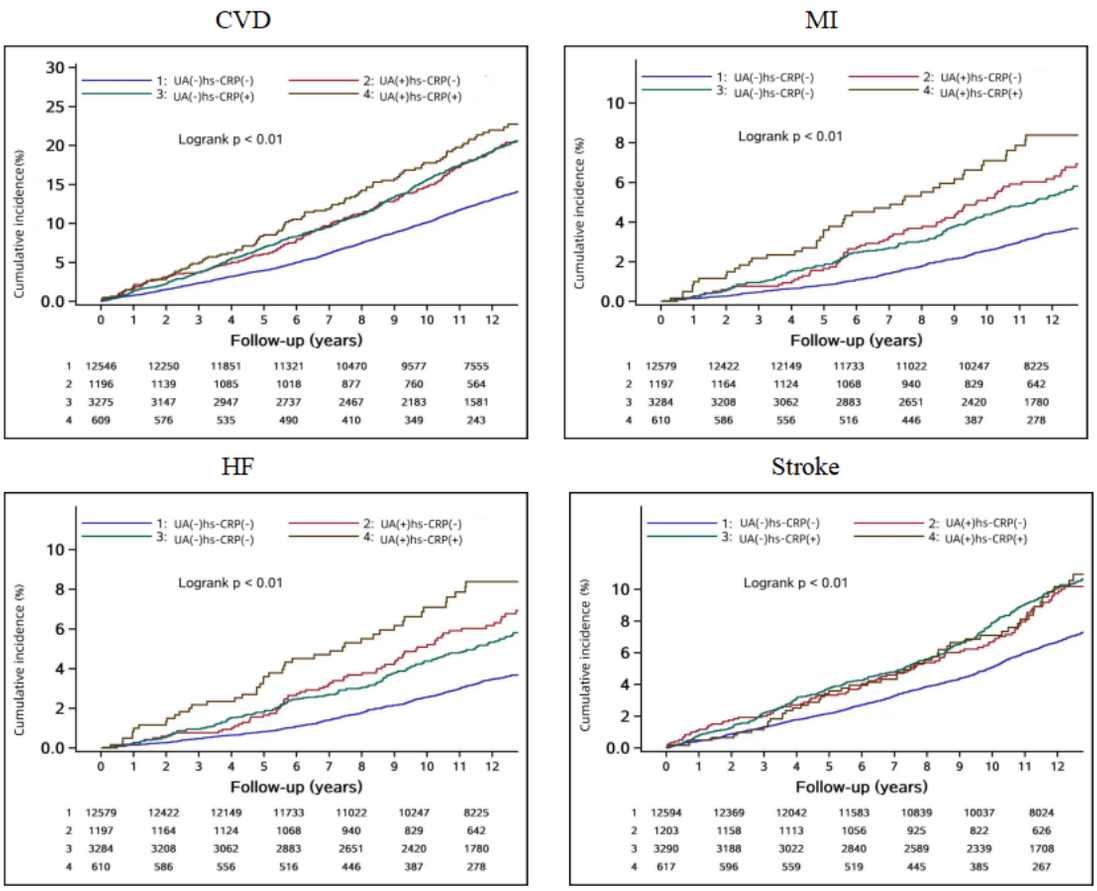

Figure 1. Cumulative incidence of uric acid and hs-CRP and CVD subtypes in chronic kidney disease

Multivariate Cox proportional hazard regression model was used to analyze the relationship between each group and CVD and subtypes (Table 2). After correction, the HR (95%CI) of CVD in UA(+)hs-CRP(-), UA(-)hs-CRP(+) and UA(+) hs-CRP(+) group were 1.27 (1.10-1.46), 1.25 (1.14-1.38), and 1.34 (1.11-1.61), respectively, compared with the low uric acid low hs-CRP group. UA and hs-CRP had a combined effect on the risk of CVD (P for interaction < 0.05).

Table 2. Relationship between uric acid and hs-CRP and risk of cardiovascular disease in chronic kidney disease

	UA(-) hs-CRP(-)	UA(+) hs-CRP(-)	UA(-) hs-CRP(+)	UA(+) hs-CRP(+)	
CVD					
N(%)	1751(13.94)	229(19.02)	616(18.72)	129(20.90)	
Incidence rate	12.02	18.11	17.70	21.47	
Model 1 (95%CI)	Ref.	1.41(1.23-1.62)	1.35(1.22-1.48)	1.48(1.24-1.79)	
Model 2 (95%CI)	Ref.	1.36(1.18-1.59)	1.31(1.19-1.44)	1.44(1.19-1.73)	
Model 3 (95%CI)	Ref.	1.28(1.11-1.47)	1.25(1.14-1.38)	1.34(1.11-1.62)	
Model 4 (95%CI)	Ref.	1.27(1.10-1.46)	1.25(1.14-1.38)	1.34(1.11-1.61)	
P for interaction					0.02
MI					
N(%)	263(2.09)	32(2.66)	118(3.59)	24(3.89)	
Incidence rate	1.72	2.34	3.18	3.68	
Model 1 (95%CI)	Ref.	1.29(0.89-1.86)	1.67(1.33-2.09)	1.77(1.15-2.72)	
Model 2 (95%CI)	Ref.	1.28(0.89-1.86)	1.62(1.29-2.04)	1.74(1.13-2.69)	
Model 3 (95%CI)	Ref.	1.21(0.83-1.75)	1.55(1.26-1.99)	1.57(1.02-2.43)	
Model 4 (95%CI)	Ref.	1.18(0.81-1.71)	1.55(1.23-1.94)	1.57(1.01-2.42)	

	UA(-) hs-CRP(-)	UA(+) hs-CRP(-)	UA(-) hs-CRP(+)	UA(+) hs-CRP(+)
HF				
N(%)	447(3.55)	77(6.39)	173(5.26)	51(8.26)
Incidence rate	2.94	5.74	4.68	7.99
Model 1 (95%CI)	Ref.	1.80(1.38-2.28)	1.40(1.16-1.68)	2.10(1.56-2.86)
Model 2 (95%CI)	Ref.	1.76(1.37-2.28)	1.36(1.13-1.64)	2.01(1.13-2.87)
Model 3 (95%CI)	Ref.	1.64(1.27-2.12)	1.28(1.07-1.55)	1.93(1.41-2.65)
Model 4 (95%CI)	Ref.	1.61(1.25-2.09)	1.31(1.09-1.58)	1.92(1.40-2.63)
Stroke				
N(%)	868(6.89)	109(9.05)	305(9.27)	55(8.91)
Incidence rate	5.78	8.22	8.41	8.61
Model 1 (95%CI)	Ref.	1.33(1.09-1.62)	1.33(1.17-1.52)	1.31(0.97-1.72)
Model 2 (95%CI)	Ref.	1.27(1.04-1.56)	1.30(1.14-1.48)	1.26(0.95-1.65)
Model 3 (95%CI)	Ref.	1.19(1.01-1.49)	1.24(1.09-1.42)	1.17(0.88-1.53)
Model 4 (95%CI)	Ref.	1.19(1.01-1.48)	1.23(1.08-1.41)	1.16(0.88-1.54)

Note: Model 1: corrects for age and sex. Model 2: Smoking, alcohol consumption, education level and body mass index were adjusted on the basis of Model 1. Model 3: On the basis of model 2, we corrected hypertension, diabetes, LDL-C, proteinuria, antihypertensive drugs, lipid-lowering drugs and hypoglycemic drugs. Model 4: eGFR is corrected on the basis of Model 3.

3.3 Hierarchical analysis of CVD by different groups

Stratified analysis showed (Figure 2) that UA and hs-CRP were more strongly correlated with CVD risk in female patients compared with male patients, patients < 65 years old compared with patients ≥65 years old, and patients who smoked compared with non-smoking patients (P for interaction < 0.05). No interaction was observed between alcohol consumption (yes or no) and eGFR (≥45 or < 45 mL/min/1.73m^2) stratification factors (P for interaction > 0.05).

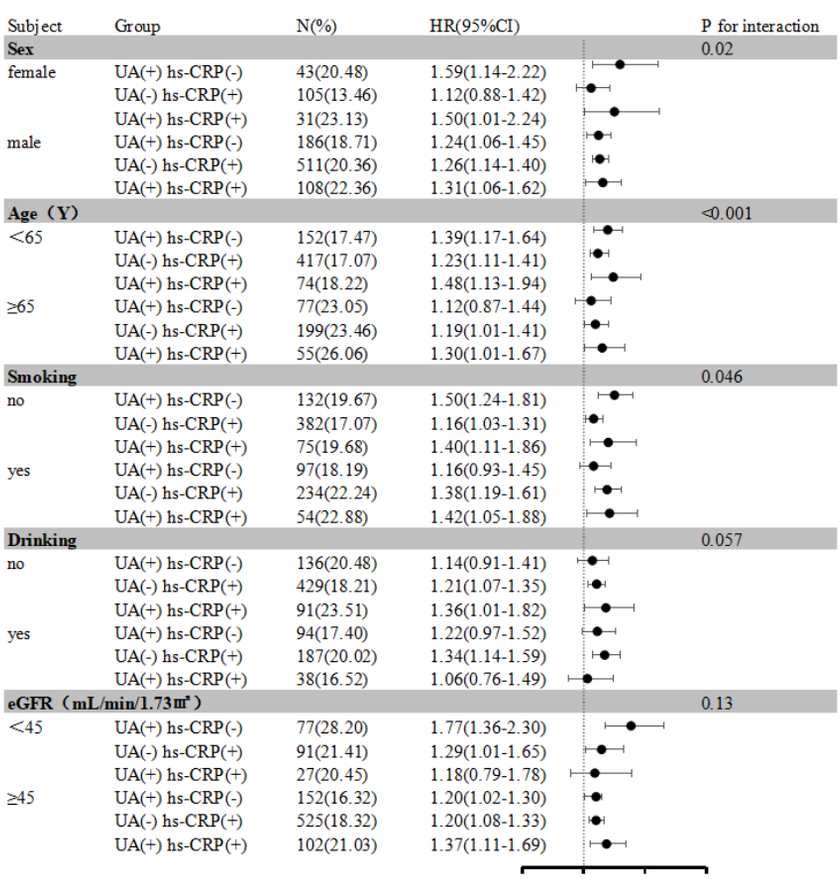

Figure 2. Stratified analysis of uric acid and hs-CRP and the risk of cardiovascular disease in chronic kidney disease

Note: Corrected model: age, sex, smoking, alcohol consumption, education level, body mass index, hypertension, diabetes, LDL-C, proteinuria, antihypertensive drugs, lipid-lowering drugs, hypoglycemic drugs, eGFR.

4. Discussion

In this study, 17,708 patients with chronic kidney disease in the Kailuan study were followed up for an average of (11.24±3.74) years, and it was found that high UA and high hs-CRP had a combined effect on the risk of CVD in CKD patients, and the risk of CVD was greater when they were uniformly increased than when they were only increased. Additionally, the association between high UA and high hs-CRP and cardiovascular disease risk in patients with CKD was independent of patients' baseline eGFR levels.

Our results confirm previous studies suggesting that UA and hs-CRP are risk factors for cardiovascular disease in the CKD population, and in this study, after adjusting for potential confounders, high UA and high hs-CRP alone were associated with a 27% and 25% increased risk of CVD, respectively, compared with low UA and low hs-CRP. When both levels were uniformly elevated, the risk of CVD increased by 34%, higher than the CVD risk associated with high UA alone and high hs-CRP alone. There is clinical and basic research evidence that UA and hs-CRP are positively correlated with the development of CVD [15,16]. We found that high UA and high hs-CRP had a combined effect on CVD risk in CKD patients, and combined exposure increased the risk of CVD in CKD population more than any single exposure factor. Hyperuricemia is not only a common disease in CKD patients, but also an important factor exacerbating their risk of CVD [5-7]. While CKD is generally considered to be a highly inflammatory state, the level of inflammation marked by hs-CRP can combine with uric acid to further increase the risk of CVD in this population.Therefore, in addition to focusing on creatinine levels, the management of hs-CRP and UA should be integrated into the comprehensive care of CKD patients. It may play a key role in reducing their overall cardiovascular risk and improving health outcomes.

Previous studies have shown that in the general population, the relationship between hyperuricemia and coronary heart disease and heart failure is relatively consistent [16], while the relationship between hyperuricemia and stroke is inconsistent [17]. Holme also found that the correlation between UA and heart failure in the general population was stronger than that between stroke [16]. Patients with high hs-CRP have a greater risk of coronary heart disease and heart failure than stroke [18]. Combined exposure in this study increased the risk of myocardial infarction and heart failure by 57% and 92%, respectively. High hs-CRP alone increased the risk of myocardial infarction and heart failure by 55% and 31%, compared with 23% for stroke. High uric acid alone increased the risk of heart failure by 61%, higher than the 19% risk of stroke. We extend our previous findings to patients with CKD, which may have important clinical implications and public health implications for the prevention and management of CVD in patients with CKD, particularly for myocardial infarction and heart failure.

In this study, stratified analysis showed that when UA and hs-CRP were uniformly elevated, the risk of CVD was higher in female patients than in male patients, and the risk of CVD was higher in patients < 65 years old than in patients ≥65 years old. Dugani found that the younger the age of onset of metabolic syndrome in the general population, the higher the risk of adverse cardiovascular outcomes. [19] Ramos found in the general population that serum uric acid level is an important independent risk factor for cardiovascular events in female subjects, but not in male[20].

The advantages of this study are large sample size, prospective study design, and long follow-up time. However, some limitations must be acknowledged: (1) Given that this is an observational study, the causal relationship between UA and hs-CRP and CVD risk in patients with CKD cannot be established. (2) Our diagnosis of CKD was based on a single eGFR measure and one-time strip test without follow-up assessment after 3 months (3) This study was based on the Kailuan study, in which more than 70% of participants were men from the Kailuan community, which may limit the generalizability of our results across gender composition populations.

In conclusion, this study suggests that high levels of combined UA and hs-CRP exposure are associated with an increased risk of myocardial infarction and heart failure in patients with CKD. Therefore, regular monitoring of UA and hs-CRP in patients with CKD could serve as a useful tool for identifying individuals at high risk of developing cardiovascular disease, thereby enhancing potential intervention strategies for disease prevention.

Conflict of Interest

All authors declare that there is no conflict of interest

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