# Effect of Serum Uric Acid Levels on New-Onset Atrioventricular Block: A Postprint of a Prospective Cohort Study

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## Abstract

Background Previous studies have demonstrated that serum uric acid (SUA) levels are associated with various cardiovascular diseases, such as hypertension, atrial fibrillation, heart failure, and coronary heart disease. However, the relationship between SUA and atrioventricular block remains unclear.

Objective To investigate the impact of SUA levels on new-onset atrioventricular block.

Methods This study employed a prospective cohort design. A total of 87,913 individuals who participated in health examinations during 2006–2007 and met the inclusion and exclusion criteria were enrolled as the study cohort. Based on baseline serum uric acid levels, participants were divided into a non-hyperuricemia group (SUA $\leq$ 420 mol/L) with 82,418 cases and a hyperuricemia group (SUA $>$ 420 mol/L) with 5,495 cases, with follow-up conducted biennially. New-onset atrioventricular block was designated as the endpoint event, and follow-up continued through December 31, 2019. Multivariate Cox stepwise regression models were utilized to analyze the effects of different SUA level groupings and each 1-standard deviation (SD) increase in SUA on new-onset atrioventricular block.

Results After a median follow-up period of 11.89 (9.06–12.83) years, among the 87,913 enrolled participants, 69,101 were male (78.60%) and 18,812 were female (21.40%), with a mean age of (50.71 $\pm$ 12.04) years; a total of 1,037 individuals developed atrioventricular block. After adjusting for age, sex, and other confounding factors, the hyperuricemia group exhibited a 26% increased risk of new-onset atrioventricular block compared with the non-hyperuricemia group (HR = 1.26, 95%CI = 1.02–1.54, P = 0.030), and each 1-standard deviation increase in SUA level was associated with a 12% increased risk (HR = 1.12,

95%CI = 1.05–1.19, P < 0.001). The hyperuricemia group showed a 29% increased risk of new-onset first-degree atrioventricular block compared with the non-hyperuricemia group (HR = 1.29, 95%CI = 1.05–1.60, P = 0.017), and each 1-standard deviation increase in SUA level was associated with a 12% increased risk (HR = 1.12, 95%CI = 1.05–1.20, P < 0.001). Spline function curve analysis revealed a non-linear correlation between SUA levels and new-onset atrioventricular block (P < 0.001).

Conclusion Hyperuricemia is an independent risk factor for new-onset atrioventricular block, and a dose-response relationship exists between the two.

## Full Text

# The Impact of Serum Uric Acid Levels on New-Onset Atrioventricular Block: A Prospective Cohort Study

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### Abstract

**Background:** Previous studies have shown that elevated serum uric acid (SUA) level is associated with various cardiovascular diseases, such as hypertension, atrial fibrillation, heart failure, and coronary artery disease, but its relationship with cardiac conduction system disorders remains unclear.

**Objective:** The present community-based cohort study aimed to elucidate the effects of SUA on the risk of developing atrioventricular (AV) block.

**Methods:** The Kailuan Study is a prospective cohort study based on a community population. A total of 87,913 eligible participants who participated in health examinations between 2006 and 2007 were included as the study cohort. The participants were divided into non-hyperuricemia group (SUA $\leq$ 420 mol/L) and hyperuricemia group (SUA > 420 mol/L). Follow-ups were conducted every two years until December 31, 2019. The endpoint event was defined as new-onset AV block. Multivariate Cox proportional hazard models were used to analyze the impact of different SUA levels and each 1-standard deviation (SD) increase in SUA on new-onset AV block.

**Results:** During a median follow-up of 11.89 (9.06–12.83) years, among the 87,913 participants [69,101 males (78.60%) and 18,812 females (21.40%), with a

mean age of 50.71 ± 12.04 years], 1,037 AV block cases developed. After adjusting for confounding factors, the hyperuricemia group showed a 26% increased risk of incident AV block compared to the non-hyperuricemia group (HR = 1.26, 95% CI = 1.02–1.54, P = 0.030). For each 1-SD increase in SUA level, the risk of incident AV block increased by 12% (HR = 1.12, 95% CI = 1.05–1.19, P < 0.001). Specifically, the hyperuricemia group had a 29% increased risk of incident first-degree AV block compared to the non-hyperuricemia group (HR = 1.29, 95% CI = 1.05–1.60, P = 0.017), and each 1-SD increase in SUA level was associated with a 12% increased risk of incident first-degree AV block (HR = 1.12, 95% CI = 1.05–1.20, P < 0.001). The restricted cubic spline analysis showed a nonlinear relationship between serum UA levels and the risk of developing AV block (P < 0.001).

**Conclusion:** High SUA level is an independent risk factor for AV block, and SUA level is dose-dependently associated with the risk of AV block.

**Keywords:** Atrioventricular block; First-degree atrioventricular block; Serum uric acid; Hyperuricemia; Cohort studies; Prospective studies; Root cause analysis

## Introduction

Atrioventricular (AV) block is a common cardiac disorder resulting from impaired electrical impulse conduction between the atria and ventricles. Although mild AV block was once considered benign, subsequent studies have demonstrated that prolonged PR interval is associated with multiple adverse cardiac outcomes, including atrial fibrillation, heart failure, and death. Even after permanent pacemaker implantation, patients with AV block still face higher mortality risk compared to those without AV block.

Despite the serious consequences of AV block, research on its risk factors remains limited. A Chinese cross-sectional study identified aging, male sex, low heart rate, high BMI, hypertension, diabetes, and low high-density lipoprotein cholesterol as factors associated with AV block. Autopsy studies have revealed that conduction system fibrosis is the primary pathological manifestation of conduction disorders, with inflammation serving as a precursor to fibrosis. Elevated serum uric acid (SUA) levels can trigger inflammatory responses and oxidative stress in the body. Numerous studies have established that elevated SUA is an independent risk factor for cardiovascular mortality and is closely associated with the development of hypertension, atrial fibrillation, myocardial infarction, and heart failure. Therefore, we hypothesized that elevated SUA levels might also be associated with the development of AV block. This study utilized the Kailuan Study cohort to analyze the relationship between SUA levels and new-onset AV block, providing direction for future research on the correlation between these two conditions.

This study was approved by the Ethics Committee of Kailuan General Hospital (Approval No.: [2006] Medical Ethics No. 5), and all participants provided informed consent.

## Methods

### Study Population

This prospective cohort study was conducted among employees (active and retired) of the Kailuan Group who underwent health examinations at 11 hospitals affiliated with Kailuan Group between 2006 and 2007. The examination included SUA measurement and 12-lead electrocardiogram (ECG), with follow-up examinations conducted every two years (seven follow-up waves completed to date). Participants who met the following inclusion criteria were selected: (1) attended the 2006–2007 health examination; (2) had complete baseline SUA and ECG data; and (3) agreed to participate and signed informed consent. Exclusion criteria were: (1) baseline ECG indicating AV block (2006–2007); (2) history of pacemaker implantation or use of beta-blockers or non-dihydropyridine medications; and (3) missing ECG data during follow-up.

### Data Collection

**Epidemiological Survey:** Trained professionals collected information on age, sex, smoking, alcohol consumption, physical exercise, and self-reported medical history (e.g., hypertension, diabetes) through questionnaires. Trained nurses measured height, weight, and blood pressure. BMI was calculated as weight (kg) divided by height (m) squared.

**Biochemical Measurements:** Fasting venous blood samples (5 mL) were collected between 7:00–9:00 AM. Biochemical indicators, including SUA, fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), serum creatinine, and high-sensitivity C-reactive protein (hs-CRP), were measured by the central laboratory of Kailuan Hospital using an automatic analyzer (Hitachi 747; Hitachi, Tokyo, Japan). SUA was measured using the oxidase method, with intra- and inter-assay coefficients of variation $\leq 6\%$.

**ECG Examination:** After resting supine for 5 minutes in a quiet room, participants underwent 10-second 12-lead ECG recording using an EDAN digital 12-channel ECG machine (Model SE-1201). ECG interpretation and diagnosis were performed by two cardiology specialists.

### Diagnostic Criteria

**AV Block:** First-degree AV block was defined as PR interval $\geq 0.20$ s on ECG with all atrial impulses conducted to the ventricles. Second-degree AV block was defined as partial failure of atrial impulses to conduct to the ventricles.

Third-degree AV block was defined as complete failure of all atrial impulses to conduct to the ventricles, representing complete AV pathway block.

**Hypertension:** Systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg (1 mmHg = 0.133 kPa), or documented history of hypertension or use of antihypertensive medication.

**Diabetes:** FBG $\geq$ 7.0 mmol/L, or FBG $<$ 7.0 mmol/L with documented diabetes history or use of hypoglycemic agents.

**Smoking, Alcohol Consumption, and Physical Exercise:** Smoking was defined as $\geq$ 1 cigarette per day on average in the past year. Alcohol consumption was defined as daily alcohol intake at least once per day in the past year. Physical exercise was defined as $\geq$ 3 sessions per week, with each session lasting $\geq$ 30 minutes.

**Estimated Glomerular Filtration Rate (eGFR):** Calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

**Acute Myocardial Infarction (AMI), Heart Failure, and Atrial Fibrillation:** Confirmed by attending physicians from hospital records. Myocardial infarction was diagnosed according to the 2018 Universal Definition of Myocardial Infarction. Heart failure was diagnosed based on European Society of Cardiology guidelines. Atrial fibrillation was diagnosed based on ECG showing absolutely irregular RR intervals without distinct P waves.

### Follow-up and Grouping

The baseline health examination marked the start of follow-up. The endpoint was defined as new-onset AV block or pacemaker implantation due to AV block. Follow-up ended at the occurrence of AV block, death, or the last follow-up date (December 31, 2019). Participants were divided into two groups based on baseline SUA levels: non-hyperuricemia group (82,418 participants with SUA $\leq$ 420 mol/L) and hyperuricemia group (5,495 participants with SUA $>$ 420 mol/L).

### Statistical Analysis

Data were analyzed using SPSS 13.0 statistical software. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using non-parametric tests. Categorical variables were expressed as frequency (percentage) and compared using chi-square test. Statistical significance was set at $P < 0.05$ (two-tailed test).

Survival curves were plotted with follow-up duration on the x-axis and cumulative incidence of AV block on the y-axis to observe differences between groups. Multivariate Cox stepwise regression models were used to analyze the impact

of different SUA level groups and each 1-SD increase in SUA on new-onset AV block. Time-dependent multivariate Cox stepwise regression models were used to analyze the effect of different SUA level groups on new-onset AV block.

**Sensitivity Analyses:** To minimize the influence of specific populations, we performed multivariate Cox stepwise regression analyses after excluding participants with: eGFR $< 45$ mL $\cdot$ min$^{-1}$ $\cdot$ (1.73 m$^2$)$^{-1}$, those who experienced endpoint events within 2 years, those taking diuretics, those with gout history, those with baseline or incident atrial fibrillation, and those with baseline or incident heart failure.

**Competing Risk Model:** Based on the Fine-Gray model, we performed multivariate Cox regression analysis after controlling for the competing risk of death.

**Spline Function Analysis:** After adjusting for age and sex, we plotted spline function curves to examine the relationship between SUA levels and new-onset AV block risk, observing whether a linear relationship existed.

## Results

### Baseline Characteristics

A total of 101,510 individuals participated in the 2006–2007 health examination. Among them, 99,555 had complete SUA and ECG data. After excluding 3,947 individuals with baseline ECG showing AV block, 398 with pacemaker implantation or use of beta-blockers/non-dihydropyridine medications, and 7,297 with missing ECG data during follow-up, 87,913 participants were finally included (69,101 males [78.60%] and 18,812 females [21.40%]; mean age 50.71 $\pm$ 12.04 years).

Comparison between groups revealed that the hyperuricemia group had significantly higher proportions of males, smokers, alcohol consumers, physically active individuals, hypertensive patients, those with baseline myocardial infarction, and those taking antihypertensive, lipid-lowering, and diuretic medications ($P < 0.05$). The hyperuricemia group also showed higher age, BMI, SBP, DBP, TG, TC, LDL-C, hs-CRP, and SUA levels ($P < 0.05$). In contrast, the hyperuricemia group had lower FBG levels, eGFR values, and diabetes prevalence compared to the non-hyperuricemia group ($P < 0.05$). There was no significant difference in the proportion of participants taking hypoglycemic agents between the two groups ($P > 0.05$) .

### Survival Curve Analysis of New-Onset AV Block by SUA Levels

During a median follow-up of 11.89 (9.06–12.83) years, 1,037 participants developed AV block among the 87,913 participants, with an incidence density of 11.03 per 10,000 person-years. Specifically, 965 participants developed new-onset first-degree AV block, 72 developed second-degree or higher AV block, and 37 received permanent pacemaker implantation due to AV block. The non-

hyperuricemia group had 931 cases (incidence density: 10.54 per 10,000 person-years; cumulative incidence: 3.28%), while the hyperuricemia group had 106 cases (incidence density: 18.62 per 10,000 person-years; cumulative incidence: 6.09%). The cumulative incidence of new-onset AV block and first-degree AV block was significantly higher in the hyperuricemia group compared to the non-hyperuricemia group ($P < 0.001$). However, there was no significant difference in the cumulative incidence of second-degree or higher AV block between the two groups ($P > 0.05$) [Figure 1: see original paper].

### Multivariate Cox Regression Analysis of SUA Levels on New-Onset AV Block

Using new-onset AV block (yes = 1, no = 0) as the dependent variable and SUA level grouping (non-hyperuricemia = 0, hyperuricemia = 1) and each 1-SD increase in SUA (continuous variable) as independent variables, we performed multivariate Cox regression analysis after adjusting for age, sex, and other confounders. The results showed that the hyperuricemia group had a 26% increased risk of new-onset AV block compared to the non-hyperuricemia group (HR = 1.26, 95% CI = 1.02–1.54, P = 0.030). Each 1-SD increase in SUA level was associated with a 12% increased risk of new-onset AV block (HR = 1.12, 95% CI = 1.05–1.19, $P < 0.001$). For first-degree AV block, the hyperuricemia group showed a 29% increased risk (HR = 1.29, 95% CI = 1.05–1.60, P = 0.017), and each 1-SD increase in SUA level increased the risk by 12% (HR = 1.12, 95% CI = 1.05–1.20, $P < 0.001$). No significant associations were found for second-degree or higher AV block ($P > 0.05$) .

### Time-Dependent Cox Regression Analysis

Using time-dependent Cox regression analysis with new-onset AV block as the dependent variable and SUA level grouping as the independent variable (adjusted for age, sex, and other confounders), the results were consistent with those from the multivariate Cox regression model .

### Stratified Analysis by Age and Sex

After stratifying by age, no significant differences were observed in the risk of new-onset AV block between hyperuricemia and non-hyperuricemia groups in either age stratum ($P > 0.05$) .

After stratifying by sex, multivariate Cox regression analysis revealed that in males, the hyperuricemia group had a 24% increased risk of new-onset AV block compared to the non-hyperuricemia group (HR = 1.24, 95% CI = 1.00–1.53, P = 0.049). However, no significant difference was observed between the two groups in females ($P > 0.05$) .

### Sensitivity Analyses

After excluding participants with baseline eGFR $< 45$ mL $\cdot$ min$^{-1}$ $\cdot$ (1.73 m$^2$)$^{-1}$, those with endpoint events within 2 years, those taking diuretics, those with gout history, those with baseline or incident atrial fibrillation, and those with baseline or incident heart failure, the multivariate Cox regression analysis yielded results consistent with the main model. After excluding participants with gout history, the analysis showed that before adjusting for medication use (Model 2), the hyperuricemia group had a 28% increased risk of new-onset AV block (HR = 1.28, 95% CI = 1.04–1.58, P = 0.020). However, after further adjustment for medication use, the difference between groups was no longer statistically significant (P $>$ 0.05), while each 1-SD increase in SUA level remained associated with an 11% increased risk (HR = 1.11, 95% CI = 1.05–1.18, P $<$ 0.001) .

### Competing Risk Model Analysis

A total of 9,830 all-cause deaths (11.2%) occurred during follow-up. Using the Fine-Gray model to control for the competing risk of death, the results remained consistent with those from the multivariate Cox regression model .

### Spline Function Curve Analysis

Restricted cubic spline analysis with knots at the 5th, 35th, 65th, and 95th percentiles of SUA levels revealed a nonlinear relationship between SUA levels and the risk of new-onset AV block (P $<$ 0.001) [Figure 2: see original paper].

## Discussion

The key finding of this study is that hyperuricemia is a risk factor for new-onset AV block. The increased risk of AV block associated with hyperuricemia is independent of traditional risk factors and demonstrates a dose-response relationship. Additionally, the effect of hyperuricemia on AV block risk may be sex-dependent, and medications for hypertension, glucose, and lipid metabolism disorders may attenuate the risk of AV block caused by hyperuricemia.

Over 11 years of follow-up, we found that the hyperuricemia group had a 26% higher risk of developing AV block compared to the non-hyperuricemia group, with a clear dose-response relationship: each 1-SD increase in SUA level (81.81 mol/L) increased AV block risk by 12%. The spline function curve analysis also demonstrated a nonlinear relationship between SUA levels and new-onset AV block risk. Although few previous studies have examined the effect of SUA levels on AV block, cross-sectional and longitudinal studies have identified hypertension and diabetes as risk factors for AV block, with OR values of 1.08 and 1.20, respectively, and an HR of 1.63 for third-degree AV block. Our findings suggest that the risk of AV block associated with hyperuricemia may be higher than that of traditional risk factors, expanding our understanding of uric acid-induced cardiovascular damage.

The pathophysiological mechanism linking elevated SUA to AV block remains unclear. We hypothesize that hyperuricemia may promote AV block by inducing myocardial fibrosis and apoptosis. Early studies have confirmed that the most common pathological process in permanent AV block is idiopathic bilateral bundle branch fibrosis. Recent research by YANNI et al. in rats with ischemic heart failure and AV nodal conduction dysfunction found significantly increased collagen content in the AV node and right AV ring, suggesting that fibrosis is the primary pathological change underlying conduction dysfunction. Uric acid acts as a pro-oxidant in the cytoplasm, causing oxidative stress that promotes myocardial fibrosis and apoptosis. Accumulating evidence links oxidative stress to cardiac hypertrophy, myocardial fibrosis, and remodeling. In hyperuricemic rats, researchers have observed abnormal myocardial cell morphology, myocardial fibrosis, and apoptosis. BERGAMINI et al. also observed increased xanthine oxidase expression and free radical production in hyperuricemic patients, leading to impaired oxidative metabolism associated with myocardial fibrosis and ventricular remodeling. Subsequent studies demonstrated that uric acid induces cardiomyocyte apoptosis and interstitial fibrosis by activating calpain-1 and endoplasmic reticulum stress.

This study also found that the effect of hyperuricemia on AV block may be sex-dependent. In males, hyperuricemia increased the risk of new-onset AV block by 24%, whereas no significant association was observed in females. A large-scale cross-sectional study from Japan showed that increased SUA levels were significantly associated with atrial fibrillation in both sexes. However, a Swedish study confirmed that hyperuricemia increased diabetes risk only in males, consistent with our findings. Other studies have reported that elevated SUA was associated with increased risk of atherosclerosis and diabetes only in females. The pathogenic risk of hyperuricemia in different sexes requires further investigation. We did not find age-dependent effects of hyperuricemia on AV block risk.

Since severe renal insufficiency, gout history, and diuretic use can elevate SUA levels, and atrial fibrillation and heart failure history may be associated with AV block development, we excluded these populations and those with endpoint events within 2 years of follow-up. The positive association between hyperuricemia and AV block remained unchanged, indicating that our findings are robust.

Our study has several limitations. First, the study population was from a single cohort in northern China with a predominantly male composition, which may limit generalizability. Second, although we adjusted for lifestyle factors such as smoking, alcohol consumption, and physical exercise, we lacked assessment of potential risk factors like education level and dietary habits. Third, AV block is a chronic progressive disease, and our median follow-up of 11.89 years may have been insufficient to detect an association between SUA levels and second-degree or higher AV block.

In conclusion, this study has important clinical and public health implications.

First, we identified hyperuricemia as a risk factor for AV block and found that the risk associated with short-term hyperuricemia is higher, suggesting that controlling SUA levels may yield benefits in a short period. Second, we found that antihypertensive, hypoglycemic, and lipid-lowering medications can attenuate the risk of AV block caused by hyperuricemia, indicating that patients with hyperuricemia and comorbid hypertension, diabetes, or hyperlipidemia should receive comprehensive treatment. Finally, controlling SUA levels can reduce not only AV block risk but also broader cardiovascular disease risk, underscoring the significant public health importance of SUA management.

**Author Contributions:** WU Yuntao and WU Shouling conceptualized the research direction and study design. ZHU Chenrui, LI Na, ZHAO Haiyan, HUANG Zhe, LIU Yan, and JI Chunpeng were responsible for data collection, organization, and statistical analysis. ZHU Chenrui drafted the manuscript. WU Yuntao and WU Shouling revised and reviewed the manuscript.

**Conflict of Interest:** The authors declare no conflict of interest.

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*Note: Figure translations are in progress. See original paper for figures.*