

# Hyperuricemia Increases the Risk of Postoperative Recurrence in Chinese Patients with Chronic Rhinosinusitis

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**Background:** Elevated serum uric acid is crucial in the pathophysiology of chronic inflammatory diseases. However, its impact on chronic rhinosinusitis (CRS) recurrence risk is unknown. This study investigates the association between elevated serum uric acid and the risk of CRS recurrence.

**Methods:** A retrospective cohort study was conducted on 1004 CRS patients (including 638 males and 366 females) who received functional endoscopic sinus surgery. All patients were followed up for more than 2 years, and categorized into subgroups based on phenotype, gender, and postoperative recurrence. Cox regression analysis was performed to evaluate the associations between serum uric acid and the risk of CRS recurrence.

**Results:** After categorization, 104 males had hyperuricemia, and 54 females presented hyperuricemia. The rate of recurrent CRS in the hyperuricemia group was significantly higher compared to the non-hyperuricemia group in both males and females ( $P < 0.05$ ). In both male and female patients, the rate of hyperuricemia and uric acid levels were elevated in the recurrent CRS group in comparison with the non-recurrent CRS group ( $P < 0.05$ ). Unadjusted and adjusted Cox regression analysis demonstrated that serum uric acid was an independent risk factor for CRS recurrence ( $P < 0.05$ ). The receiver operator characteristic curve showed that serum uric acid was a potential biomarker for predicting the recurrence of CRS and its phenotypes in both genders ( $P < 0.05$ ).

**Conclusion:** There is a close relationship between elevated serum uric acid and the recurrence risk of CRS and its phenotypes, suggesting that serum uric acid may be a novel biomarker for predicting recurrent CRS.

**Keywords:** chronic rhinosinusitis, uric acid, hyperuricemia, biomarker, recurrence

## Introduction

Chronic rhinosinusitis (CRS) is a prevalent condition characterized by ongoing inflammation in the nasal and paranasal sinus mucosa.<sup>1,2</sup> It is estimated that CRS affects more than 10% of the adult population in Europe and the USA, and the prevalence continues to increase.<sup>3</sup> CRS can be categorized into CRS without nasal polyps (CRSsNP), and CRS with nasal polyps (CRSwNP), referring to nasal endoscopic findings.<sup>4,5</sup> Both phenotypes present a high disease burden on individuals, families, and societies and impair physical, social, and emotional health.<sup>6,7</sup> Although enormous efforts have been made in the understanding of CRS pathophysiology, its exact pathological mechanism is still unclear.

Currently, the treatment of CRS includes medical and surgical therapy, and functional endoscopic sinus surgery (FESS) is the mainstay for CRS patients who are refractory to medical management.<sup>8,9</sup> FESS can remove polyps and inflammatory tissues, open obstructed sinus to create larger ventilation space, reduce the antigenic load, and then facilitate the delivery of postoperative topical medications.<sup>1,10</sup> Although FESS can provide immediate and long-term symptom relief and improve the quality of life in most CRS patients, a certain proportion of them still suffer the risk of

recurrence during the postoperative follow-up.<sup>11,12</sup> It has been reported that the postoperative recurrence rate of CRS ranges from 12% to 50%, posing challenges to its management.<sup>13</sup> Although several indicators and factors were demonstrated to be associated with CRS relapse, including asthma, computed tomography (CT) score, CRS endotype, previous surgery, and serum IgE level, the underlying mechanisms were still poorly recognized.<sup>14–16</sup> Hence, it is of utmost clinical significance and urgency to identify patients who are at higher risk of treatment failure and postoperative recurrence after FESS, as well as to investigate the risk factors associated with relapse.

Uric acid is the end-product of purine metabolism and its levels are regulated by the enzyme xanthine oxidase.<sup>17,18</sup> It is widely recognized that various factors including age, renal function, diet, and notably gender can affect uric acid concentrations. Disturbances in uric acid metabolism can have considerable health implications.<sup>19,20</sup> Emerging evidence from numerous studies indicates that uric acid plays a pivotal role in the development of various chronic inflammatory diseases and autoimmune disorders.<sup>21–24</sup> Elevated levels of uric acid have been observed in systemic lupus erythematosus, and these increased levels are linked to disease severity. Additionally, hyperuricemia has been demonstrated to worsen renal damage in lupus patients, thus affecting their overall prognosis.<sup>23,24</sup> Both experimental and clinical data have provided evidence supporting the notion that hyperuricemia can induce dysregulated intestinal immunity, impair the integrity of the intestinal barrier, stimulate systemic inflammation, and further elevate uric acid levels, all of which contribute to the pathogenesis of inflammatory bowel disease.<sup>22,25</sup> Recent research has highlighted the significance of purine metabolism and uric acid metabolism in the immunopathogenesis of airway inflammatory diseases. Elevated levels of serum uric acid have been identified as a risk factor for developing asthma.<sup>17,18</sup> However, there is limited knowledge regarding the relationship between serum uric acid and CRS, and whether increased uric acid levels can independently contribute to CRS recurrence remains uncertain. Further investigation is warranted to elucidate the potential association and independent impact of elevated uric acid levels on CRS recurrence.

To clarify this aspect and better characterize recurrent factors, we conducted the present retrospective analysis of clinical data from CRS patients undergoing FESS. We investigated the associations between elevated uric acid, hyperuricemia, and the risk of CRS recurrence, and identified whether serum uric acid could serve as a novel biomarker in predicting postoperative recurrence.

## Methods

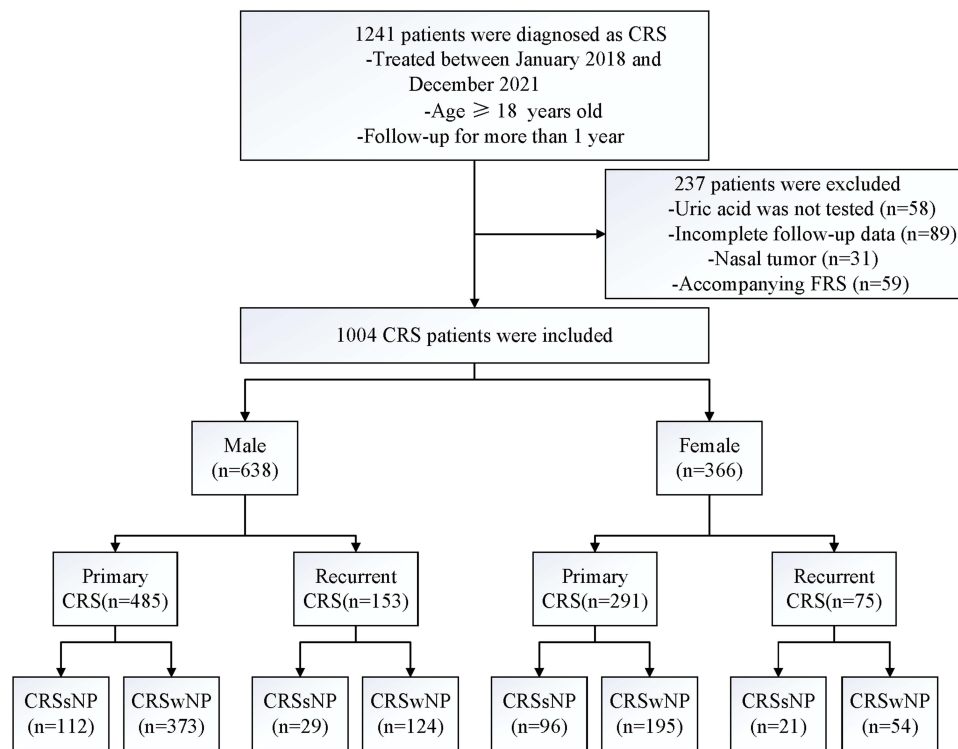
### Patients and Settings

The present retrospective study was approved by the Human Ethical Committee in Xiangya Hospital of Central South University (protocol no.202209212). This study complies with the Declaration of Helsinki. As this retrospective study did not involve any patient's private information or commercial interests, it was deemed exempt from requiring informed consent by the Ethics Committee. The study design and participant selection are presented as a flow chart in [Figure 1](#). CRS patients who underwent FESS at our medical center between January 2018 and December 2021 were enrolled in this study. All CRS patients met the diagnostic criteria provided by the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS 2012) and required FESS because of failed medical treatment.<sup>26</sup> Clinical diagnosis was made based on physical examination, clinical symptoms, nasal endoscopy findings, and sinus CT scan. We excluded the following patients: incomplete clinical data; accompanied with fungal sinusitis, allergic fungal rhinosinusitis, or sinonasal benign or malignant tumors; current acute inflammation; previous radiotherapy; aged < 18 years or >70 years.

After FESS, all postoperative CRS patients were instructed to follow a treatment regimen that included daily nasal saline irrigation, antibiotics, topical corticosteroids, and periodic endoscopic debridement. Regular follow-up appointments were scheduled for patients, during which endoscopic examinations were performed to monitor their progress. Recurrence was defined by reappeared clinical symptoms, endoscopic signs, and/or CT evidence for at least 2 months despite the rescue regimen of antibiotics and oral steroids as previously described.<sup>27,28</sup> Based on a minimum follow-up period of 2 years, the patients were categorized into two groups: the recurrent group and the non-recurrent group.

### Clinical Data Collection and Group Settings

The baseline characteristics and clinical data were obtained from the electronic clinical records. The following preoperative data were collected: gender, age, body mass index (BMI), smoking, diabetes mellitus, hypertension, hyperlipidemia,



**Figure 1** Flowchart classification of the CRS cohort.

**Abbreviations:** CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

hyperuricemia, and CRS phenotype. BMI was calculated as body weight (kg) divided by the square of the height (m). Laboratory data including uric acid, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), peripheral blood eosinophil count and percentage were measured in the clinical laboratory and biochemistry department. Comorbidities were diagnosed as previous publications described.<sup>29–32</sup> Hypertension was defined as repeated SBP  $\geq 140$  and/or DBP  $\geq 90$  mmHg or ongoing anti-hypertensive medications. Diabetes mellitus was diagnosed when FBG  $\geq 7.0$  mmol/L, 2-h plasma glucose  $\geq 11.1$  mmol/L, or current consumption of hypoglycemic drugs. Hyperlipidemia was diagnosed when TC  $\geq 5.72$  mmol/L, TG  $\geq 1.70$  mmol/L, or a determinate anamnesis. Hyperuricemia was diagnosed as a serum uric acid level  $\geq 7.0$  mg/dL in males and  $\geq 6.0$  mg/dL in females. Based on serum uric acid levels, both male and female patients with CRS were divided into the non-hyperuricemia group and hyperuricemia group, and variable differences were compared between the two groups in males and females, respectively.

## Statistical Analysis

Data are expressed as numbers and percentages for categorical variables and compared utilizing the chi-squared test. Quantitative variables with normal distribution are shown as mean  $\pm$  standard deviation and compared with the Student's *t*-test between the two groups. Those data without normal distribution were presented as median and interquartile ranges (IQRs), and the Mann–Whitney *U*-test was utilized for comparison. The interactions were evaluated by multi-factor analysis of variance. Significant interactions were observed between gender, serum uric acid, and CRS recurrence in this study. Therefore, all analyses were conducted stratified by the two gender groups. Patients were categorized into recurrent CRS and non-recurrent groups, and Cox proportional hazards models were performed, considering serum uric acid as a continuous variable to explore its association with the risk of CRS recurrence in different adjusted models. Receiver operator characteristic (ROC) curves were constructed to evaluate the potential ability of serum uric acid to predict postoperative recurrence. Statistical significance was regarded as a two-tailed  $P < 0.05$ . All the analyses were applied with SPSS version 22.0 (IBM, Chicago, IL, USA).

## Results

### Characteristics and Baseline Data of the Study Subjects

Initially, 1241 CRS patients who underwent FESS were enrolled, and 237 subjects were excluded from the exclusion criteria. Eventually, a total of 1004 eligible patients, including 638 males and 366 females, were included in the present study (Figure 1). The baseline characteristics and clinical data of the study subjects are displayed in Table 1. After categorizing individuals by gender and serum uric acid levels, we compared the rates of recurrent CRS between those with and without hyperuricemia. The results in Table 2 showed that the rate of recurrent CRS in the hyperuricemia group was significantly higher compared to the non-hyperuricemia group in both males and females ( $P<0.05$ ). Furthermore, this trend was also observed in the rate of recurrent CRSwNP in both genders ( $P<0.05$ ) but not in recurrent CRSsNP ( $P>0.05$ ).

### Serum Uric Acid Level Associated with the Risk of CRS Recurrence

To investigate the association between serum uric acid and the risk of recurrence, we further categorized study subjects into recurrent CRS and non-recurrent CRS groups. In male patients, the rate of allergic rhinitis, Lund-MacKay score, rate of hyperuricemia, uric acid levels and peripheral blood eosinophil percentage were significantly elevated in the recurrent CRS group compared to the non-recurrent CRS group ( $P<0.05$ ). The age, Lund-MacKay score, rates of diabetes mellitus and hyperuricemia, uric acid, FBG levels, and peripheral blood eosinophil percentage were increased in the recurrent CRS group in comparison to the non-recurrent CRS group in females (Table 3,  $P<0.05$ ). Moreover, Figure 2 suggested that serum uric acid levels were markedly enhanced in recurrent CRS patients compared to non-recurrent CRS patients both in males and females, and these tendencies were also observed in recurrent CRSsNP and CRSwNP patients ( $P<0.05$ ).

**Table 1** Characteristics of CRS Patients by Availability of Data

Variables	Total (n=1004)	Male (n=638)	Female (n=366)
CRSsNP/CRSwNP	266/738	151/487	117/249
Age, year	45.0 (32.0–55.0)	43.0 (31.0–55.0)	46.5 (33.0–56.0)
BMI, kg/m <sup>2</sup>	22.7 (20.8–25.2)	23.5 (21.3–25.9)	21.7 (20.0–23.9)
Alcohol consumption, n (%)	71 (7.1)	62 (9.7)	9 (2.5)
Smoking, n (%)	159 (15.8)	144 (22.6)	15 (4.1)
Allergic rhinitis, n (%)	236 (23.5)	139 (21.8)	97 (26.5)
Asthma, n (%)	158 (15.7)	90 (14.1)	68 (18.6)
VAS	7.0 (5.0–8.0)	7.0 (6.0–8.0)	6.0 (5.0–8.0)
Lund-MacKay score	15.0 (12.0–19.0)	15.0 (13.0–19.0)	14.0 (11.0–18.0)
Lund-Kennedy score	7.0 (6.0–8.0)	7.0 (6.0–8.0)	6.0 (5.0–8.0)
Diabetes mellitus, n (%)	115 (11.5)	74 (11.6)	41 (11.2)
Hypertension, n (%)	185 (18.4)	129 (20.2)	56 (15.3)
Hyperlipidemia, n (%)	172 (17.1)	108 (16.9)	64 (17.5)
Hyperuricemia, n (%)	158 (15.7)	104 (16.3)	54 (14.8)
Uric acid lowering agents, n (%)	83 (8.3)	56 (8.8)	27 (7.4)
Uric acid, mg/dL	5.7 (4.9–6.7)	6.1 (5.3–6.9)	5.2 (4.5–6.1)
SBP, mmHg	125.0 (115.0–137.0)	127.0 (118.0–138.3)	120.0 (110.0–133.0)
DBP, mmHg	80.0 (73.0–86.0)	80.0 (74.0–88.0)	77.0 (70.0–84.0)
FBG, mmol/L	4.9 (4.7–5.4)	4.9 (4.6–5.4)	4.9 (4.6–5.4)
TG, mmol/L	1.4 (1.0–2.0)	1.4 (1.0–2.1)	1.3 (0.9,1.9)
TC, mmol/L	4.8 (4.2–5.3)	4.7 (4.2–5.3)	4.8 (4.2–5.4)
HDL-C, mmol/L	1.2 (1.0–1.3)	1.1 (1.0–1.3)	1.2 (1.1–1.4)
LDL-C, mmol/L	2.9 (2.5–3.4)	2.9 (2.5–3.4)	2.9 (2.4–3.3)
Peripheral blood eosinophil count (10 <sup>9</sup> /L)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.1 (0.1–0.3)
Peripheral blood eosinophil percentage (%)	2.5 (1.1–4.9)	2.6 (1.1–5.4)	2.1 (1.0–4.4)

**Abbreviations:** CRS, chronic rhinosinusitis; BMI, body mass index; VAS, visual analogue score; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

**Table 2** Baseline Demographics and Clinical Characteristics Between Non-Hyperuricemia and Hyperuricemia Groups

Variables	Male			Female		
	Non-hyperuricemia (n=534)	Hyperuricemia (n=104)	P value	Non-hyperuricemia (n=312)	Hyperuricemia (n=54)	P value
Recurrent CRS	115 (21.5)	38 (36.5)	0.002	52 (16.7)	23 (42.6)	<0.001
Recurrent CRSsNP	22 (4.1)	7 (6.7)	0.299	18 (5.8)	3 (5.6)	1.000
Recurrent CRSwNP	93 (17.4)	31 (29.8)	0.006	34 (10.9)	20 (37.0)	<0.001
Age, year	43.0 (31.0–55.0)	43.0 (32.0–54.0)	0.762	47.0 (32.0–55.0)	50.0 (37.8–59.0)	0.308
BMI, kg/m <sup>2</sup>	23.3 (21.1–25.8)	24.2 (22.2–26.6)	0.012	21.8±2.6	22.7±2.9	0.041
Alcohol consumption, n (%)	48 (9.0)	14 (13.5)	0.055	9 (2.9)	0 (0.0)	0.367
Smoking, n (%)	112 (21.0)	32 (30.8)	0.039	14 (4.5)	1 (1.9)	0.708
Allergic rhinitis, n (%)	105 (19.7)	34 (32.7)	0.004	82 (26.3)	15 (27.8)	0.868
Asthma, n (%)	69 (12.9)	21 (20.2)	0.064	55 (17.6)	13 (24.1)	0.260
VAS	6.0 (5.0–8.0)	7.0 (6.0–8.0)	0.643	6.0 (5.0–8.0)	7.0 (5.0–9.0)	0.481
Lund-MacKay score	14.0 (12.0–18.0)	15.0 (13.0–18.0)	0.588	14.0 (11.0–18.0)	16.0 (12.0–19.0)	0.298
Lund-Kennedy score	7.0 (6.0–8.0)	7.0 (5.0–8.0)	0.623	6.0 (5.0–8.0)	7.0 (5.0–9.0)	0.632
Diabetes mellitus, n (%)	63 (11.8)	11 (10.6)	0.867	28 (9.0)	13 (24.1)	0.007
Hypertension, n (%)	97 (18.2)	32 (30.8)	0.005	43 (13.8)	13 (24.1)	0.100
Hyperlipidemia, n (%)	86 (16.1)	22 (21.2)	0.252	50 (16.0)	14 (25.9)	0.083
Uric acid, mg/dL	5.8 (5.1–6.5)	7.7 (7.3–8.1)	<0.001	5.0 (4.4–5.7)	7.0 (6.7–7.7)	<0.001
Uric acid lowering agents, n (%)	0 (0.0)	56 (53.8)	<0.001	0 (0.0)	27 (50.0)	<0.001
SBP, mmHg	126.0 (118.0–137.0)	131.0 (120.3–143.8)	0.017	120.0 (110.0–134.0)	126.0 (112.0–143.0)	0.019
DBP, mmHg	80.0 (74.0–87.0)	80.0 (75.0–92.8)	0.162	77.0 (70.0–85.0)	77.5 (70.0–84.3)	0.632
FBG, mmol/L	4.9 (4.6–5.4)	4.9 (4.5–5.5)	0.900	4.8 (4.6–5.4)	4.9 (4.6–5.7)	0.376
TG, mmol/L	1.4 (1.0–2.0)	1.5 (1.1–2.4)	0.022	1.3 (0.9–1.9)	1.5 (1.0–2.1)	0.059
TC, mmol/L	4.7 (4.2–5.3)	4.8 (4.2–5.5)	0.179	4.8 (4.2–5.4)	4.9 (4.1–5.5)	0.794
LDL-C, mmol/L	1.1 (1.0–1.3)	1.2 (1.0–1.3)	0.789	1.2 (1.0–1.4)	1.2 (1.0–1.4)	0.500
HDL-C, mmol/L	2.9 (2.4–3.4)	3.1 (2.6–3.6)	0.079	2.9 (2.4–3.3)	3.0 (2.4–3.4)	0.963
Peripheral blood eosinophil count (10 <sup>9</sup> /L)	0.1 (0.1–0.3)	0.2 (0.1–0.3)	0.164	0.1 (0.1–0.2)	0.1 (0.1–0.3)	0.336
Peripheral blood eosinophil percentage (%)	2.4 (1.0–4.7)	2.6 (1.2–5.5)	0.093	1.9 (0.9–4.0)	2.3 (1.4–4.8)	0.205

**Abbreviations:** CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; BMI, body mass index; VAS, visual analogue score; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

**Table 3** Baseline Demographics and Clinical Characteristics Between Non-Recurrent and Recurrent CRS Groups

Variables	Male			Female		
	Non-recurrent CRS (n=485)	Recurrent CRS (n=153)	P value	Non-recurrent CRS (n=291)	Recurrent CRS (n=75)	P value
CRSsNP/CRSwNP	122/363	29/124	0.315	96/195	21/54	0.488
Age, year	43.0 (31.0–55.0)	46.0 (32.0–55.0)	0.241	47.0 (32.0–55.0)	50.0 (37.0–60.0)	0.041
BMI, kg/m <sup>2</sup>	23.7±3.4	23.7±3.4	0.859	21.8±2.7	22.4±2.7	0.151
Alcohol consumption, n (%)	47 (9.7)	15 (9.8)	1.000	7 (2.4)	2 (2.7)	1.000
Smoking, n (%)	113 (23.3)	31 (20.3)	0.506	13 (4.4)	2 (2.7)	0.745
Allergic rhinitis, n (%)	94 (19.4)	45 (29.4)	0.013	75 (25.8)	22 (29.3)	0.558
Asthma, n (%)	65 (13.4)	25 (16.3)	0.354	51 (17.5)	17 (22.7)	0.320
VAS	6.0 (5.0–8.0)	7.0 (6.0–8.0)	0.202	6.0 (5.0–7.0)	7.0 (6.0–9.0)	0.094
Lund-MacKay score	14.0 (12.0–18.0)	16.0 (14.0–19.0)	0.037	14.0 (12.0–17.0)	15.0 (12.0–19.0)	0.027
Lund-Kennedy score	6.0 (5.0–8.0)	7.0 (6.0–9.0)	0.108	7.0 (5.0–8.0)	6.0 (5.0–9.0)	0.199
Diabetes mellitus, n (%)	56 (11.5)	18 (11.8)	1.000	27 (9.3)	14 (18.7)	0.040
Hypertension, n (%)	102 (21.0)	27 (17.6)	0.419	44 (15.1)	12 (16.0)	0.858
Hyperlipemia, n (%)	84 (17.3)	24 (15.7)	0.711	50 (17.2)	14 (18.7)	0.736
Hyperuricemia, n (%)	66 (13.6)	38 (24.8)	0.002	32 (11.0)	22 (29.3)	<0.001

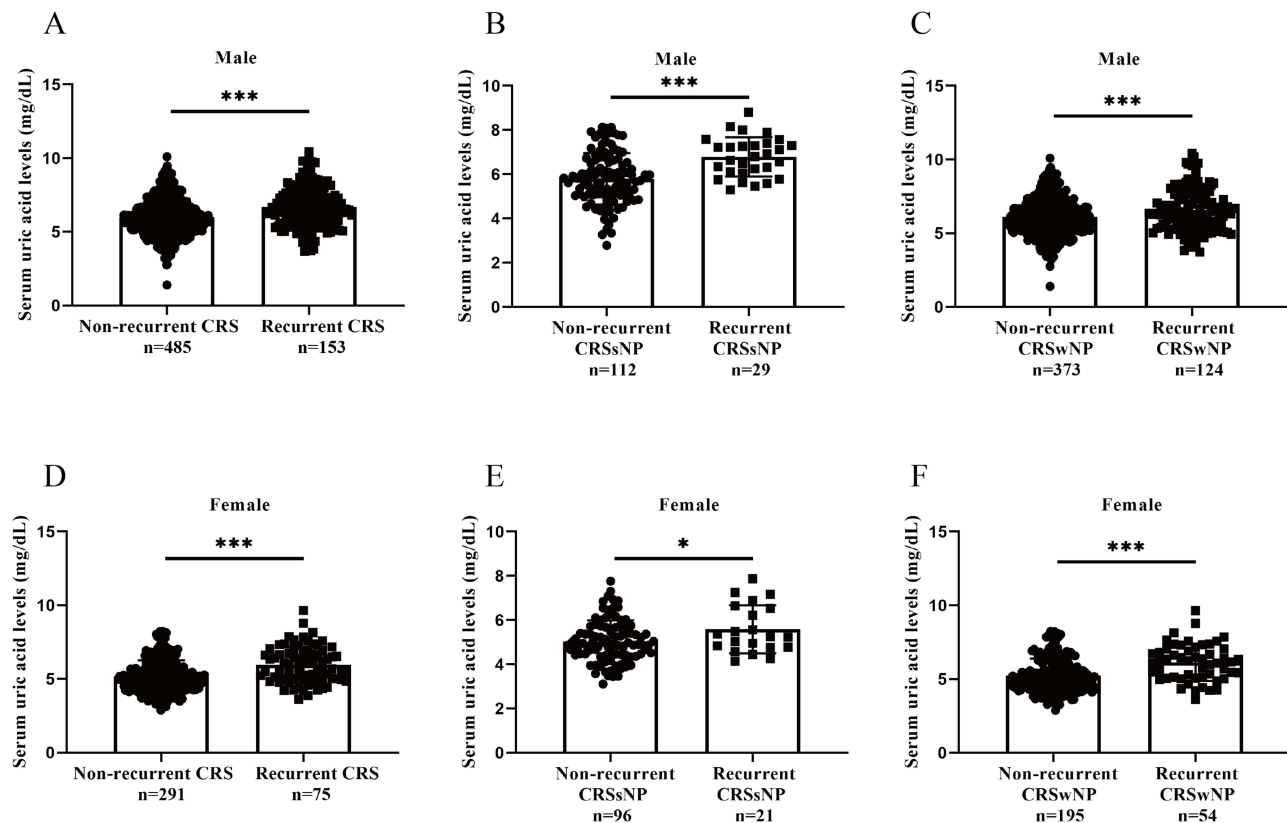
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**Table 3** (Continued).

Variables	Male			Female		
	Non-recurrent CRS (n=485)	Recurrent CRS (n=153)	P value	Non-recurrent CRS (n=291)	Recurrent CRS (n=75)	P value
Uric acid, mg/dL	6.1±1.2	6.7±1.4	<0.001	5.0 (4.4–5.7)	5.8 (5.0–6.8)	<0.001
Uric acid lowering agents, n (%)	29 (6.0)	27 (17.6)	<0.001	15 (5.2)	12 (16.0)	<0.001
SBP, mmHg	127.0 (118.0–140.0)	127.0 (117.0–136.0)	0.256	120.0 (110.0–134.0)	121.0 (114.0–131.0)	0.699
DBP, mmHg	81.4±11.6	82.2±10.5	0.465	77.0 (70.0–85.0)	76.0 (70.0–81.0)	0.097
FBG, mmol/L	4.9 (4.5–5.4)	4.9 (4.5–5.4)	0.334	4.8 (4.6–5.4)	4.9 (4.6–5.4)	0.018
TG, mmol/L	1.4 (1.0–2.1)	1.3 (0.9–2.0)	0.129	1.3 (0.9–1.9)	1.3 (0.9–1.7)	0.628
TC, mmol/L	4.8 (4.2–5.3)	4.7 (4.0–5.3)	0.577	4.8 (4.2–5.4)	5.0 (4.1–5.6)	0.343
LDL-C, mmol/L	1.1 (1.0–1.3)	1.1 (1.0–1.3)	0.752	1.2 (1.0–1.4)	1.2 (1.1–1.4)	0.718
HDL-C, mmol/L	3.0 (2.5–3.4)	3.0 (2.5–3.4)	0.705	2.9 (2.4–3.3)	3.0 (2.5–3.4)	0.816
Peripheral blood eosinophil count (10 <sup>9</sup> /L)	0.1 (0.1–0.2)	0.2 (0.1–0.3)	0.077	0.1 (0.1–0.2)	0.2 (0.1–0.3)	0.169
Peripheral blood eosinophil percentage (%)	2.1 (1.0–4.7)	2.8 (1.3–6.0)	0.002	1.8 (0.8–3.7)	2.5 (1.4–5.5)	0.017

**Abbreviations:** CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; BMI, body mass index; VAS, visual analogue score; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

We also performed unadjusted and adjusted Cox proportional hazards models to examine the association between serum uric acid and CRS recurrence. The results in Table 4 demonstrated that elevated uric acid was closely correlated with a higher risk of CRS recurrence in males and females (P<0.05), and this increase in the risk was independent of



**Figure 2** Comparisons of serum uric acid levels between non-recurrent and recurrent CRS patients and subgroups based on gender and phenotype. (A–C) male; (D–F) female. \*P<0.05, \*\*\*P<0.001.

**Abbreviations:** CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.



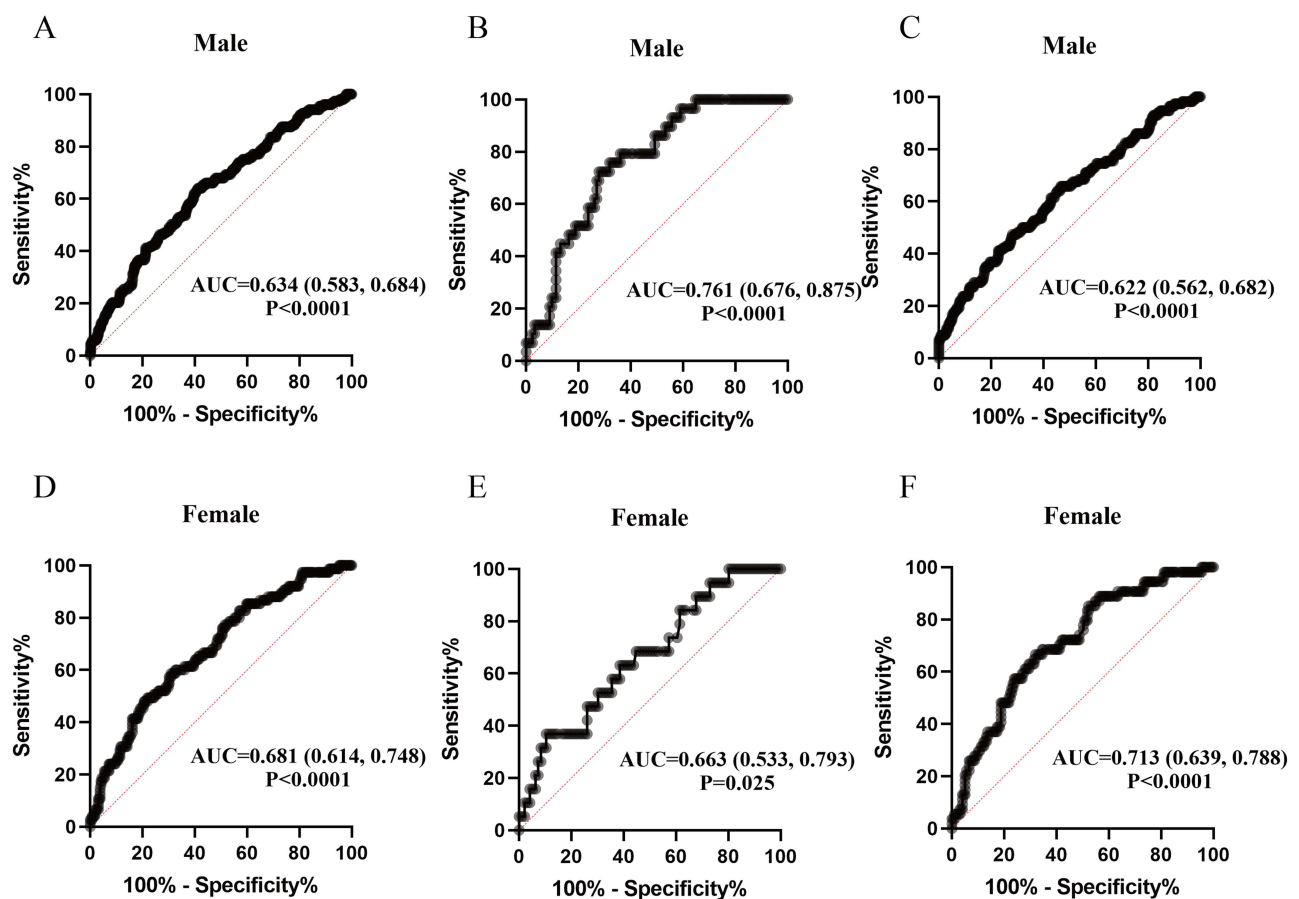
**Table 4** Cox Regression Analysis for CRS Recurrence According to Serum Uric Acid Level

Variables	Male			Female		
	HR	95% CI	P value	HR	95% CI	P value
Unadjusted	1.834	1.017–3.307	0.044	1.763	1.409–2.206	<0.0001
Model 1	2.243	1.153–4.363	0.017	1.736	1.384–2.173	<0.0001
Model 2	2.237	1.142–4.381	0.019	1.739	1.384–2.186	<0.0001
Model 3	2.133	1.021–4.449	0.042	1.721	1.377–2.172	<0.0001

**Notes:** Model 1: Adjusted for age, BMI, alcohol consumption, and smoking; Model 2: Adjusted for age, BMI, alcohol consumption, smoking, VAS, Lund-MacKay score, and Lund-Kennedy score; Model 3: Adjusted for age, BMI, alcohol consumption, smoking, VAS, Lund-MacKay score, Lund-Kennedy score, allergic rhinitis, asthma, diabetes mellitus, hypertension, hyperlipidemia, uric acid lowering agents, and peripheral blood eosinophil count and percentage.

**Abbreviations:** CRS, chronic rhinosinusitis; HR, hazard ratio; CI, confidence interval.

several potential confounders after adjusting for different models. As presented in Figure 3, ROC results suggested that serum uric acid exhibited potentiality in predicting the recurrence of CRS and its two phenotypes in both genders ( $P < 0.05$ ).



**Figure 3** ROC curves of serum uric acid in predicting recurrence of CRS and its subgroups based on gender and phenotype. (A–C) male; (D–F) female; (A and D) CRS; (B and E) CRSsNP; (C and F) CRSwNP.

**Abbreviations:** ROC, receiver operator characteristic; AUC, area under curve; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps.

## Discussion

To the best of our knowledge, this is the first study to explore the associations between serum uric acid and CRS recurrence in a Chinese population with a large sample size. The present study revealed that both CRS males and females accompanied with hyperuricemia presented a higher rate of recurrence compared to those without hyperuricemia despite CRS phenotypes. Moreover, the rate of hyperuricemia and serum uric acid levels were vastly increased in the recurrent CRS patients than in the non-recurrent CRS patients despite gender, and elevated uric acid was associated with a higher risk of CRS recurrence. This association remained significant even after adjusting for other potential risk factors, including age, BMI, alcohol, smoking, diabetes mellitus, hypertension, and hyperlipidemia.

The etiology of recurrent CRS is multifactorial and poorly understood. It was reported that recurrent CRS patients were more unresponsive to maximal medical and surgical therapy and were at the highest risk of treatment failure and repeated recurrence.<sup>33,34</sup> Therefore, it is extremely important and clinically meaningful to elucidate factors associated with the risk of CRS recurrence and examine their predictive values. Previous publications found that surgeon-related factors, anatomic variance, CRS endotype and phenotype, and other accompanying diseases were the major causes of disease recidivation.<sup>16,35</sup> Recently, peripheral blood biomarkers attracted close attention as predictors for prognosis and recurrence in CRS patients because of their objectivity, simplicity and convenience, and minimal invasion.<sup>36–38</sup> However, relatively few investigators have analyzed the effect of serum uric acid in the CRS pathogenesis, and the correlations between uric acid levels and hyperuricemia and the risk of postoperative recurrence are rarely discovered.

It was established that uric acid had a crucial proinflammatory property, and uric acid accumulation and downstream pathway activation promoted the inflammatory stress response and aggravated the disease development in various inflammatory diseases.<sup>22,25</sup> In our previous study, we found that the purine metabolism pathway was significantly changed in the serum samples of CRSwNP patients, and several downstream metabolite concentrations were associated with the CRSwNP endotypes.<sup>39</sup> Li et al<sup>40</sup> explored the metabolomic profiling in sinonasal tissue samples and identified that tissue uric acid levels were enhanced in CRS patients and associated with its subtypes. Overall, these prior findings indicated a close connection between purine metabolism, uric acid, and CRS. However, the mechanism underlying the uric acid and CRS recurrence was unclear.

In this study, we observed that serum uric acid concentrations and rate of hyperuricemia were markedly increased in recurrent CRS patients than in non-recurrent CRS subjects despite phenotype, and elevated uric acid levels were positively correlated with the risk of recurrence in both genders. Intriguingly, this correlation was independent of several confounding factors. Accordingly, severe infiltration of inflammatory cells in sinonasal mucosa, excessive proinflammatory cytokine accumulation, and tissue remodeling were regarded as the major pathogenetic mechanisms in the recurrent CRS.<sup>41,42</sup> It was worth noting that uric acid pathway activation could promote innate cytokine production and group 2 innate lymphoid cell (ILC2s) accumulation, which contributed to aggravating Th2 immune responses.<sup>43,44</sup> Emerging evidence has suggested that hyperuricemia can increase oxidative stress levels within the airway mucosa, leading to increased generation of free radicals, which in turn may trigger inflammatory responses, epithelial-mesenchymal transition, and tissue remodeling.<sup>11</sup> Experimental and clinical studies have demonstrated that IL-6, CXCL8, IL-1 $\beta$ , and epithelial-derived cytokines were enhanced in the serum samples of hyperuricemia patients, and these biomarkers were pivotal in facilitating the inflammatory responses.<sup>24</sup> Furthermore, a recent study revealed that high concentrations of soluble uric acid could promote the production of IL-1 $\beta$ , induce immune cell composition, and exacerbate the type 2 immune responses, then trigger pulmonary immunopathology and asthma development.<sup>45</sup> Collectively, we hypothesize that increased levels of serum uric acid may enhance the activation of immune cells, the release of proinflammatory cytokines, and oxidative stress. This, in turn, can lead to heightened infiltration of inflammatory cells and tissue remodeling in nasal tissues, then exacerbate the pathogenetic processes associated with CRS. Consequently, these mechanisms may contribute to the recurrence of the disease.

Concerning sex disparities indeed existing in serum uric acid levels, we performed a subgroup analysis based on gender to construct a more reliable conclusion. Our major findings presented significant clinical implications for the management of CRS patients based on data from the subgroup analysis. Although other clinical variables, including accompanying asthma, CRS phenotypes, and endotypes were identified to be associated with the risk of postoperative recurrence in CRS.<sup>15,16</sup> The presented study highlighted that both accompanying hyperuricemia and increased serum uric acid levels should be listed as potential risk factors for clinical management and evaluation of recurrence in CRS patients.



Moreover, the observation that enhanced serum uric acid remained correlated with an increased risk of CRS recurrence independent from other potential recurrent factors indicated that serum uric acid could serve as a potent predictor of postoperative recurrence. Hence, measuring serum uric acid levels could aid in determining the need for preoperative uric acid-lowering therapy in CRS patients with elevated uric acid levels. However, further multicenter prospective studies with a larger sample size are necessary to strengthen our findings and establish accurate cut-off values that can be applied in clinical settings.

Nonetheless, this study has several limitations. First, all subjects were recruited in a single medical center with the same ethnicity and region, and this may increase the risk of selection bias and limit its generalization. Second, this is a retrospective study to explore the association between serum uric acid and the risk of CRS recurrence, and their causal relationship and the underlying mechanisms are not clarified. Third, the serum uric acid levels fluctuate over time and are affected by different external factors, and these variations may impair the analysis results. Fourth, the exact disease durations of hyperuricemia and other comorbidities are not available, and this may overshadow the reliability of the results.

## Conclusion

To our knowledge, this study was the first one with a large sample size to reveal that hyperuricemia and elevated serum uric acid levels were closely associated with the risk of CRS recurrence, and serum uric acid might act as a novel and robust biomarker predicting recurrent CRS despite of phenotype and gender. These findings exhibited significant implications in preoperative uric acid management in CRS patients with high uric acid levels and facilitated its individualized treatment.

## Ethics and Consent Statements

The present retrospective study was approved by the Human Ethical Committee in Xiangya Hospital of Central South University (protocol no.202209212). This study complies with the Declaration of Helsinki. As this retrospective study did not involve any patient's private information or commercial interests, it was deemed exempt from requiring informed consent by the Ethics Committee.

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## Disclosure

The authors declare no conflict of interest in this article.

## References

1. Xu X, Seet JE, Yap QV, et al. Latent class analysis of structured histopathology in prognosticating surgical outcomes of chronic rhinosinusitis with nasal polyps in Singapore. *Rhinology*. 2023;61(4):358–367. doi:10.4193/Rhin22.455
2. Sedaghat AR, Singerman KM, Phillips KM. Discordance of chronic rhinosinusitis disease control between EPOS guidelines and patient perspectives identifies utility of patient-rated control assessment. *Rhinology*. 2022;60(6):444–452. doi:10.4193/Rhin22.160
3. Bachert C, Marple B, Schlosser RJ, et al. Adult chronic rhinosinusitis. *Nat Rev Dis Primers*. 2020;6(1):86. doi:10.1038/s41572-020-00218-1
4. Fokkens WJ, Viskens AS, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of biologics in chronic rhinosinusitis with nasal polyps 2023. *Rhinology*. 2023;61(3):194–202. doi:10.4193/Rhin22.489
5. Sedaghat AR, Fokkens WJ, Lund VJ, et al. Consensus criteria for chronic rhinosinusitis disease control: an international Delphi Study. *Rhinology*. 2023;61(6):519–530. doi:10.4193/Rhin23.335
6. de Loos DAE D, Cornet ME, Hopkins C, Fokkens WJ, Reitsma S. Measuring control of disease in chronic rhinosinusitis; assessing the correlation between SinoNasal Outcome Test-22 and visual analogue scale item scores. *Rhinology*. 2023;61(1):39–46. doi:10.4193/Rhin21.275
7. Hellings PW, Fokkens WJ, Orlandi R, et al. The EUFOREA pocket guide for chronic rhinosinusitis. *Rhinology*. 2023;61(1):85–89. doi:10.4193/Rhin22.344
8. Wu PW, Chiu CH, Huang YL, et al. Tissue eosinophilia and computed tomography features in paediatric chronic rhinosinusitis with nasal polyps requiring revision surgery. *Rhinology*. 2023;61(3):348–357. doi:10.4193/Rhin22.435

9. Ramkumar SP, Marks L, Lal D, Marino MJ. Outcomes of limited versus extensive surgery for chronic rhinosinusitis: a systematic review and meta-analysis. *Int Forum Allergy Rhinol.* 2023;13(11):2096–2100. doi:10.1002/alr.23178
10. Khanwalkar A, Chan E, Rooddar P, et al. Tranexamic acid does not significantly lower postoperative bleeding after endoscopic sinus and nasal surgery. *Int Forum Allergy Rhinol.* 2023;13(9):1584–1591. doi:10.1002/alr.23127
11. Xie S, Zhang C, Xie Z, Zhang J, Zhang H, Jiang W. Serum metabolomics identifies uric acid as a possible novel biomarker for predicting recurrence of chronic rhinosinusitis with nasal polyps. *Rhinology.* 2023;61(6):541–551. doi:10.4193/Rhin23.236
12. Jo S, Lee SH, Jo HR, et al. Eosinophil-derived TGFβ1 controls the new bone formation in chronic rhinosinusitis with nasal polyps. *Rhinology.* 2023;61(4):338–347. doi:10.4193/Rhin22.439
13. Kim DH, Han JS, Kim GJ, Basurrah MA, Hwang SH. Clinical predictors of polyps recurring in patients with chronic rhinosinusitis and nasal polyps: a systematic review and meta-analysis. *Rhinology.* 2023;61(6):482–497. doi:10.4193/Rhin23.136
14. Bai J, Huang JH, Price CPE, et al. Prognostic factors for polyp recurrence in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol.* 2022;150(2):352–361.e357. doi:10.1016/j.jaci.2022.02.029
15. Sella GCP, Tamashiro E, Sella JA, et al. Asthma is the dominant factor for recurrence in chronic rhinosinusitis. *J Allergy Clin Immunol Pract.* 2020;8(1):302–309. doi:10.1016/j.jaip.2019.08.007
16. Hong SN, Kim YS, Cha H, et al. Endotype-related recurrence pattern of chronic rhinosinusitis in revision functional endoscopic sinus surgery. *Auris Nasus Larynx.* 2022;49(2):215–221. doi:10.1016/j.anl.2021.07.010
17. Tao JL, Chen YZ, Dai QG, et al. Urine metabolic profiles in paediatric asthma. *Respirology.* 2019;24(6):572–581. doi:10.1111/resp.13479
18. Wang H, Jia Y, Yi M, Li Y, Chen O. High serum uric acid was a risk factor for incident asthma: an open cohort study. *Risk Manag Healthc Policy.* 2020;13:2337–2346. doi:10.2147/RMHP.S277463
19. Mei Y, Dong B, Geng Z, Xu L. Excess uric acid induces gouty nephropathy through crystal formation: a review of recent insights. *Front Endocrinol.* 2022;13:911968. doi:10.3389/fendo.2022.911968
20. Ramos GK, Goldfarb DS. Update on uric acid and the kidney. *Curr Rheumatol Rep.* 2022;24(5):132–138. doi:10.1007/s11926-022-01069-3
21. Calich AL, Borba EF, Ugolini-Lopes MR, da Rocha LF, Bonfã E, Fuller R. Serum uric acid levels are associated with lupus nephritis in patients with normal renal function. *Clin Rheumatol.* 2018;37(5):1223–1228. doi:10.1007/s10067-018-3991-8
22. Lv Q, Xu D, Zhang X, et al. Association of hyperuricemia with immune disorders and intestinal barrier dysfunction. *Front Physiol.* 2020;11:524236. doi:10.3389/fphys.2020.524236
23. Dos Santos M, Veronese FV, Moresco RN. Uric acid and kidney damage in systemic lupus erythematosus. *Clin Chim Acta.* 2020;508:197–205. doi:10.1016/j.cca.2020.05.034
24. Wang X, Liu X, Qi Y, et al. High level of serum uric acid induced monocyte inflammation is related to coronary calcium deposition in the middle-aged and elder population of China: a five-year prospective cohort study. *J Inflamm Res.* 2022;15:1859–1872. doi:10.2147/JIR.S353883
25. Lv Q, Xu D, Ma J, et al. Uric acid drives intestinal barrier dysfunction through TSP0-mediated NLRP3 inflammasome activation. *Inflamm Res.* 2021;70(1):127–137. doi:10.1007/s00011-020-01409-y
26. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl.* 2012;23:3 p preceding table of contents, 1–298.
27. Qi S, Yan B, Liu C, Wang C, Zhang L. Predictive significance of Charcot-Leyden Crystal mRNA levels in nasal brushing for nasal polyp recurrence. *Rhinology.* 2020;58(2):166–174. doi:10.4193/Rhin19.296
28. Brescia G, Contro G, Giacomelli L, Barion U, Frigo AC, Marioni G. Blood eosinophilic and basophilic trends in recurring and non-recurring eosinophilic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy.* 2021;35(3):296–301. doi:10.1177/1945892420953960
29. Xue B, Johnson AK. Sensitization of hypertension: the impact of earlier life challenges: excellence award for hypertension research 2021. *Hypertension.* 2022;80(1):101161hypertensionaha12218550.
30. Lambrinoudaki I, Paschou SA, Armeni E, Goulis DG. The interplay between diabetes mellitus and menopause: clinical implications. *Nat Rev Endocrinol.* 2022;18(10):608–622. doi:10.1038/s41574-022-00708-0
31. Sun F, Zhao W, Shen H, et al. Design of smart aggregates: towards rapid clinical diagnosis of hyperlipidemia in human blood. *Adv Mater.* 2022;34(49):e2207671. doi:10.1002/adma.202207671
32. Crawley WT, Jungels CG, Stenmark KR, Fini MA. U-shaped association of uric acid to overall-cause mortality and its impact on clinical management of hyperuricemia. *Redox Biol.* 2022;51:102271. doi:10.1016/j.redox.2022.102271
33. Yilmaz G, Eyigor H, Gur OE, et al. The role of TAS2R38 genotype in surgical outcomes and culturable bacteria in chronic rhinosinusitis with or without nasal polyps. *Rhinology.* 2023;61(1):54–60. doi:10.4193/Rhin22.118
34. Xie S, Jiang S, Fan R, et al. Elevated body mass index increased the risk of recurrence in Chinese patients with chronic rhinosinusitis. *Am J Otolaryngol.* 2023;44(4):103841. doi:10.1016/j.amjoto.2023.103841
35. Veloso-Teles R, Cerejeira R. Endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps: clinical outcome and predictive factors of recurrence. *Am J Rhinol Allergy.* 2017;31(1):56–62. doi:10.2500/ajra.2017.31.4402
36. Bayer K, Hamidovic S, Brkic FF, Besser G, Mueller CA, Liu DT. Peripheral eosinophil count and eosinophil-to-lymphocyte ratio are associated with revision sinus surgery. *Eur Arch Otorhinolaryngol.* 2022;280(1):183–190. doi:10.1007/s00405-022-07497-2
37. Lu PC, Lee TJ, Huang CC, Chang PH, Chen YW, Fu CH. Serum eosinophil cationic protein: a prognostic factor for early postoperative recurrence of nasal polyps. *Int Forum Allergy Rhinol.* 2021;11(4):766–772. doi:10.1002/alr.22664
38. Oka A, Ninomiya T, Fujiwara T, et al. Serum IgG4 as a biomarker reflecting pathophysiology and post-operative recurrence in chronic rhinosinusitis. *Allergol Int.* 2020;69(3):417–423. doi:10.1016/j.alit.2019.12.004
39. Xie S, Zhang H, Liu Y, et al. The role of serum metabolomics in distinguishing chronic rhinosinusitis with nasal polyp phenotypes. *Front Mol Biosci.* 2020;7:593976. doi:10.3389/fmolb.2020.593976
40. Li JX, Wang ZZ, Zhai GT, et al. Untargeted metabolomic profiling identifies disease-specific and outcome-related signatures in chronic rhinosinusitis. *J Allergy Clin Immunol.* 2022;150(3):727–735.e726. doi:10.1016/j.jaci.2022.04.006
41. Zhu KZ, He C, Li Z, et al. Development and multicenter validation of a novel radiomics-based model for identifying eosinophilic chronic rhinosinusitis with nasal polyps. *Rhinology.* 2023;61(2):132–143. doi:10.4193/Rhin22.361
42. Porras-Gonzalez C, Palacios-Garcia JM, Sanchez-Gomez S, et al. Transcriptional analysis of nasal polyps fibroblasts reveals a new source of pro-inflammatory signaling in CRSwNP. *Rhinology.* 2023;61(2):180–189. doi:10.4193/Rhin22.309

43. Fonseca W, Malinczak CA, Schuler CF, et al. Uric acid pathway activation during respiratory virus infection promotes Th2 immune response via innate cytokine production and ILC2 accumulation. *Mucosal Immunol.* 2020;13(4):691–701. doi:10.1038/s41385-020-0264-z
44. Liu X, Li Y, Li Z, et al. A novel IgG1 monoclonal antibody against xanthine oxidase alleviates inflammation induced by potassium oxonate in mice. *Int J Biol Macromol.* 2018;112:537–547. doi:10.1016/j.ijbiomac.2018.01.171
45. Schuler C, Malinczak CA, Best SKK, et al. Inhibition of uric acid or IL-1 $\beta$  ameliorates respiratory syncytial virus immunopathology and development of asthma. *Allergy.* 2020;75(9):2279–2293. doi:10.1111/all.14310

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