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White blood cell count and the incidence of hyperuricemia: insights from a community-based study

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Abstract **Hyperuricemia (HUA) is a risk factor for chronic kidney disease (CKD). The relationship between HUA and white blood cell (WBC) count remains unknown. A sampling survey for CKD was conducted in Sanlin community in 2012 and 2014. CKD was defined as proteinuria in at least the microalbuminuric stage or an estimated GFR of 60 mL/(min·1.73 m^2). HUA was defined as serum uric acid > 420 μmol/L in men and > 360 μmol/L in women. This study included 1024 participants. The prevalence of HUA was 17.77%. Patients with HUA were more likely to have higher levels of WBC count, which was positively associated with HUA prevalence. This association was also observed in participants without CKD, diabetes mellitus, hyperlipidemia, or obesity. Multivariate logistic regression analysis showed that WBC count was independently associated with the risk for HUA in male and female participants. Compared with participants without HUA, inflammatory factors such as high-sensitivity C-reactive protein, tumor necrosis factor-α, and interleukin 6 increased in participants with HUA. Hence, WBC count is positively associated with HUA, and this association is independent of conventional risk factors for CKD.**

Keywords white blood cell count; hyperuricemia; chronic kidney disease; inflammation

Introduction

The incidence of chronic kidney disease (CKD) continuously increases, and its prevalence rate in China is 10.8%–11.8% [1,2]. Effective prevention strategies for CKD must be developed to reduce the global burden of end-stage renal disease. Hyperuricemia (HUA) is one of the known risk factors for CKD [3]. Therefore, identifying the risk factors for HUA is a good way to prevent the occurrence of CKD.

Previous studies reported that age, gender, and body mass index (BMI) are the risk factors for HUA [4]. Uric acid (UA) has been recognized to be damaging because it activates cytosolic phospholipase A2 (cPLA2), inflammatory transcription factor nuclear factor-κB [5], tumor necrosis factor, monocyte chemotactic protein-1 [6], and cyclooxygenase-2 [7]. Some clinical studies showed that UA, white blood cells (WBCs), high-sensitivity C-reactive protein (hs-CRP), and lipoproteins are positively associated with subclinical thoracic atherosclerosis [8], cardiovascular disease (CVD) [9], and metabolic syndrome [10]. Additionally, UA levels are inversely associated with neutrophil ratios in patients suffering from stroke [11]. However, the relationship between HUA and WBC remains unknown. Therefore, a community-based survey for CKD was conducted in Sanlin in 2012 and 2014. In this study, estimated GFR (eGFR) was calculated by the MDRD equation [12]. HUA was defined as serum UA $>$ 420 μmol/L in males and $>$ 360 μmol/L in females or a history of anti-HUA medication use [13]. Subjects with a diabetic history or those with fasting blood glucose $>$ 7 mmol/L or 2 h postprandial blood glucose $>$ 11 mmol/L were categorized as diabetic [1]. CVD was defined as a history of myocardial infarction, chronic heart failure, left ventricular hypertrophy, and/or stroke/TIA. Hypertension was diagnosed as systolic blood pressure (SBP) $\geqslant$ 140 mmHg or diastolic blood pressure (DBP) $\geqslant$ 90 mmHg or a history of antihypertensive medication use [14]. The survey included 1156 participants, of which 1024 provided complete information. The

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mean age of the sample was 55.86 years. The survey included 116 participants who had CKD. The prevalence of HUA was 17.77% (182/1024).

WBC counts were elevated in participants with HUA

Table 1 shows the participants' demographic characteristics and biochemical test results. In males, participants with HUA were more likely to have higher BMI ($P < 0.01$), waist hip rate (WHR; $P < 0.01$), BUN ($P = 0.01$), WBC count ($P < 0.01$), hemoglobin (Hb; $P = 0.01$), prevalence of CVD ($P = 0.02$) and hyperlipidemia ($P = 0.02$), and lower eGFR ($P < 0.01$). In females, participants with HUA were more likely to be older ($P < 0.01$) and had higher SBP ($P < 0.01$); DBP ($P < 0.01$); BMI ($P < 0.01$); WHR ($P < 0.01$); BUN ($P < 0.01$); WBC count ($P < 0.01$); prevalence of diabetes ($P = 0.03$), hypertension ($P < 0.01$), and hyperlipidemia ($P < 0.01$); and lower eGFR ($P < 0.01$).

WBC levels were positively associated with prevalence of HUA

To clarify the association between WBC levels and HUA, we classified all participants into sextile according to their WBC count: (2.80–4.80) $\times 10^9$/L, (4.81–5.49) $\times 10^9$/L, (5.50–6.07) $\times 10^9$/L, (6.08–6.76) $\times 10^9$/L, (6.77–7.74) $\times 10^9$/L, and (7.75–14.1) $\times 10^9$/L for quartile 1, 2, 3, 4, 5, and 6, respectively. We found a positive correlation between WBC count and HUA prevalence. The prevalence rate was 11.2% among participants with WBC count in the first level and increased to 13.50%, 17.60%, 12.90%, 24.7%, and 26.32% in levels 2, 3, 4, 5, and 6, respectively (P for trend < 0.01; Table 2). This finding suggests that participants with higher WBC count are more likely to have HUA.

Association between WBC count and HUA was present in participants without CKD, DM, hyperlipidemia, or obesity

To explore whether the link between WBC count and HUA is independent of CKD, DM, hyperlipidemia, and obesity, we compared the WBC count between participants without CKD, DM, hyperlipidemia, or obesity. In participants without CKD, DM, hyperlipidemia, and/or obesity, WBC counts were significantly higher in HUA participants than in non-HUA participants. The results are shown in Table 3. These results suggest that the link between WBC count and HUA is not influenced by CKD, DM, hyperlipidemia, and obesity.

Table 1 Characteristics of study cohort by HUA

	Males			Females		
	Non-HUA $N = 330$	HUA $N = 74$	P value	Non-HUA $N = 512$	HUA $N = 108$	P value
Age (year)	55.09±12.73	54.59±16.38	0.81	54.92±13.13	63.50±13.45	<0.01
SBP (mmHg)	130.85±14.37	133.18±12.97	0.20	126.85±15.22	136.23±13.47	<0.01
DBP (mmHg)	85.60±8.18	86.54±9.58	0.387	81.30±8.36	84.86±7.27	<0.01
BMI (kg/m^2)	24.54±3.48	26.30±2.97	<0.01	23.49±3.68	26.23±3.78	<0.01
WHR	0.88±0.04	0.91±0.04	<0.01	0.84±0.05	0.86±0.04	<0.01
BUN (μmol/L)	4.96±1.25	5.37±1.31	0.01	4.80±1.26	5.43±1.61	<0.01
UA (μmol/L)	331.71±51.37	469.01±42.06	<0.01	267.90±43.37	402.00±46.86	<0.01
RBC ($\times 10^{12}$/L)	4.93±0.42	5.03±0.44	0.08	4.490±0.36	4.50±0.38	0.81
WBC ($\times 10^9$/L)	6.45±1.59	7.09±1.85	<0.01	6.02±1.53	6.64±1.6	<0.01
Hb (g/L)	152.27±12.78	155.81±11.90	0.03	134.71±11.07	135.01±12.97	0.81
eGFR (mL/(min·1.73m^2))	105.36±18.61	97.86±22.28	<0.01	100.78±16.52	88.55±18.16	<0.01
CVD (None:Yes)	301:29	60:14	0.02	449:63	92:16	0.43
Smoking (None:Yes)	117:213	30:44	0.43	507:5	107:1	0.88
Drinking (None:Yes)	170:160	39:35	0.85	504:8	103:5	0.06
Gym (None:Yes)	137:193	34:40	0.82	242:270	50:58	0.45
Hypertension (None:Yes)	225:105	48:26	0.58	405:107	66:42	<0.01
DM (None:Yes)	265:65	63:11	0.34	426:86	80:28	0.03
Hyperlipidemia (None:Yes)	154:176	23:51	0.02	238:274	27:81	<0.01

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist hip rate; RBC, red blood cell; WBC, white blood cell; Hb, hemoglobin; CVD, cardiovascular disease; DM, diabetes mellitus.

Table 2 Association of WBC levels with prevalence of HUA

WBC ($\times 10^9$/L)	Total	HUA	PR%	PR	χ^2	*P* value
Quartile 1 (2.80–4.80)	170	19	11.20	1.00		
Quartile 2 (4.81–5.49)	170	23	13.50	1.21		
Quartile 3 (5.50–6.07)	170	30	17.60	1.57		
Quartile 4 (6.08–6.76)	170	22	12.90	1.15		
Quartile 5 (6.77–7.74)	170	42	24.70	2.21		
Quartile 6 (7.75–14.1)	171	45	26.32	2.35	21.9	<0.01

PR%, prevalence rate; PR, prevalence ratio.

Table 3 WBC levels in patients without CKD, DM, hyperlipidemia, or obesity

	Non-HUA		HUA		*P* value
	N	WBC	*N*	WBC	
Without CKD	758	6.19±1.60	147	6.74±1.56	*P*<0.01
Without DM	690	6.16±1.58	142	6.67±1.57	*P* = 0.001
Without hyperlipidemia	391	6.16±1.69	50	6.97±1.91	*P* = 0.002
BMI<25 kg/m^2	527	6.10±1.60	63	6.98±1.77	*P*<0.01
Without CKD, DM, hyperlipidemia, and BMI⩾25 kg/m^2	234	6.08±1.71	16	6.98±1.41	*P* = 0.04

CKD, chronic kidney disease; DM, diabetes mellitus.

Elevated WBC counts were independently associated with increased risk of HUA

Fig. 1 shows that after adjustment for age, WBC, SBP, DBP, BMI, WHR, BUN, Hb, red blood cell (RBC), eGFR, medical history (CVD, hypertension, DM, and hyperlipidemia), and health-related behaviors (cigarette smoking, alcohol drinking, and gym), participants with high WBC counts remained at increased risk for HUA (*P* for trend < 0.01).

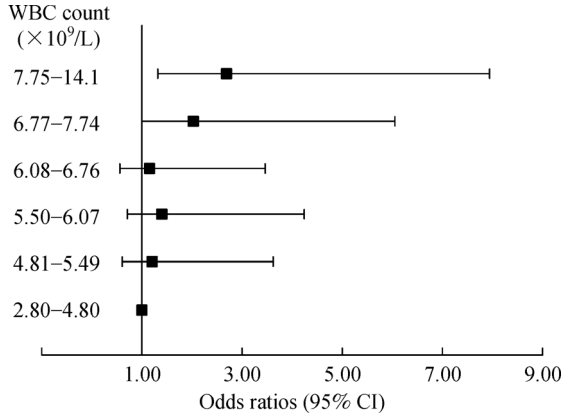

Fig. 1 Multivariate-adjusted OR and 95% CI for HUA by quintiles of WBC count in 1021 participates. The analysis was adjusted for age, WBC, SBP, DBP, BMI, WHR, BUN, Hb, RBC, eGFR, medical history (CVD, hypertension, DM, and hyperlipidemia), and health-related behaviors (cigarette smoking, alcohol drinking, and gym). OR estimates were obtained using the lowest quintile of WBC count as the reference. *P* for trend < 0.05.

Gender is one of the major factors closely associated with HUA, so we divided the group by gender. To explore whether elevated WBC count was independently associated with increased risk for HUA, we performed a multivariate logistic regression analysis in four models adjusting for different variables. These models yielded similar findings. WBC count was a strong risk factor for HUA in males and females (Table 4). Additionally, we performed logistic regression in non-elderly (age < 60 years) and elderly (age ⩾ 60 years) participants. We found that WBC count was significantly associated with risk for HUA in non-elderly (OR (95% CI) = 1.25 (1.08–1.43), *P* < 0.01) and elderly (OR (95% CI) = 1.36 (1.09–1.69), *P* = 0.01) participants.

Inflammatory factors were increased in participants with HUA

WBC is an indicator of inflammation. We selected 81 participants randomly from the cohort. We detected the serum hs-CRP, tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and IL-10 in participants with HUA (*N* = 38) and without HUA (*N* = 43). Compared with participants without HUA, Ln(hs-CRP) (4.04 ± 0.84 ng/mL vs. 3.09 ± 1.31 ng/mL, *P* < 0.01), TNF-α (3.42 ± 0.62 pg/mL vs. 2.14 ± 0.16 pg/mL, *P* = 0.05), and IL-6 (11.69 ± 2.31 pg/mL vs. 5.14 ± 1.74 pg/mL, *P* = 0.03) in participants with HUA were upregulated.

Table 4 Comparison of parameters between HUA and normal subjects by multivariate logistic regression model

	Males				Females			
	Adjusted OR	95% CI	*P* value	AIC	Adjusted OR	95% CI	*P* value	AIC
Model 1	1.24	1.07–1.43	<0.01	382.19	1.31	1.25–1.49	<0.01	523.34
Model 2	1.26	1.07–1.48	<0.01	356.00	1.28	1.11–1.49	<0.01	460.31
Model 3	1.27	1.08–1.50	<0.01	346.90	1.27	1.10–1.48	<0.01	463.44
Model 4	1.27	1.07–1.50	<0.01	348.23	1.28	1.09–1.50	<0.01	439.61

Model 1 was adjusted for age and WBC count. Model 2 was adjusted for age, WBC count, and laboratory tests (SBP, DBP, BMI, WHR, BUN, Hb, RBC, and eGFR). Model 3 was adjusted for age, WBC count, laboratory tests, and medical history (CVD, hypertension, DM, and hyperlipidemia). Model 4 was adjusted for age, WBC count, laboratory tests, medical history, and health-related behaviors (cigarette smoking, alcohol drinking, and gym).

However, no significant difference in IL-10 ($P = 0.71$) was observed between participants with HUA and without HUA (Fig. 2).

Discussion

This cross-sectional study revealed that compared with non-HUA patients, HUA patients had higher levels of WBC counts. Moreover, further analysis showed that WBC count was positively associated with incidence of HUA. This relationship was independent of age, gender, health-related behaviors (smoking, drinking, and gym), medical history (CVD, hypertension, DM, hyperlipidemia), and laboratory tests (SBP, DBP, BMI, BUN, Hb, WBC, eGFR). This study also found that WBC count was a risk factor for HUA independent of conventional CKD risk factors.

Previous studies showed that age, gender, BMI, WHR, and CVD were risk factors for HUA. Recently, circulating inflammatory cell counts and atherosclerosis were independently related with UA [15]. Su *et al.* [16] analyzed 522 male and 255 female subjects and found a significant relationship between the level of UA and WBC count, RBC count, and Hb. In our study, we found that WBC count was positively associated with the incidence of HUA by logistic analysis, and this association was independent of conventional CKD risk factors. Furthermore, we checked our conclusion by linear regression in our data. When adjusted for age, SBP, DBP, BMI, WHR, and WBC count, Hb and WBC were independent risk factors. However, when adjusted for age, SBP, DBP, BMI, WHR, WBC and RBC count, and eGFR, WBC was an independent risk factor. We confirmed that WBC count was an important independent risk factor for HUA in people with or without CKD.

The role of WBC count in other diseases has been studied. An analysis that involved 18 907 subjects over the age of 65 years showed that WBC was associated with metabolic syndrome regardless of gender [17]. Consistent with this result, a strong relationship between WBC count and features of metabolic syndrome independent of smoking in Japanese men was found [18]. Also, previous study found that elevated WBC count was associated with arterial stiffness [19]. Additionally, a similar relationship was found in diseases such as stroke [11], diabetes [20,21], hypertension [22], and CVD [23].

WBCs function as "cleaner," and they clear inflammatory cytokines. They are an indicator of inflammation. We found that compared with participants without HUA, inflammatory factors such as TNF-α and IL-6 were increased in participants with HUA. However, the

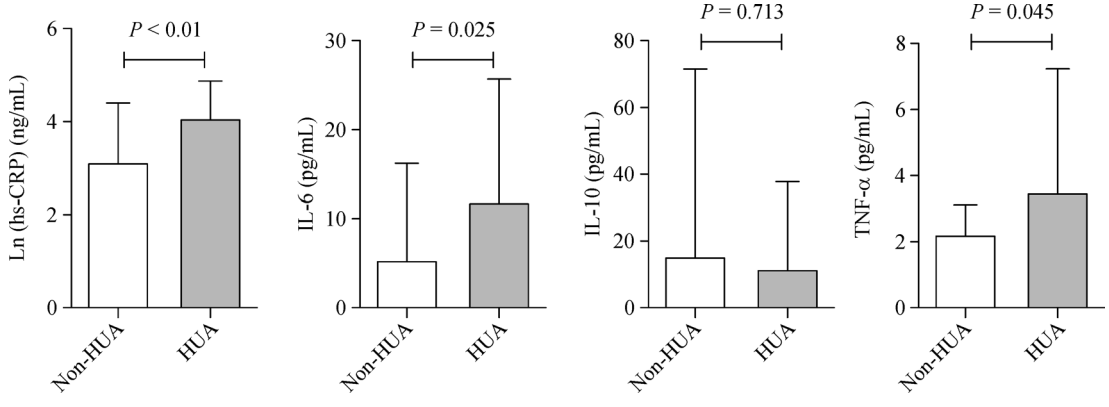

Fig. 2 Serum inflammatory factors in participants with HUA and without HUA.

mechanism by which UA influences the inflammation is unknown. Under physiological concentrations, UA is a powerful antioxidant that can scavenge superoxides, hydroxyl radicals, and singlet oxygen [24]. UA also acts as a proinflammatory factor and activates cytoplasmic phospholipase A2 and inflammatory transcription factors in renal proximal tubule cells [5]. Other studies reported that increasing serum UA levels are accompanied with TNF-α [25], monocyte chemotactic protein-1 in the kidney [6], and cyclooxygenase-2 in blood vessels [7]. Ruggiero *et al*. found that UA was positively and significantly associated with several inflammatory markers in 957 healthy elderly subjects [26]. These studies indicated that the relationship between WBC count and HUA can be explained by the activation of inflammation.

Summary

This cross-sectional study, involving a large Chinese population, revealed that WBC count was positively associated with HUA, and this association was independent of CKD conventional risk factors.

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Compliance with ethics guidelines

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