Original Article

Survey on uric acid in Chinese subjects with essential hypertension (SUCCESS): a nationwide cross-sectional study

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Background: Hyperuricemia (HUA) is associated with hypertension and increased cardiovascular risk. Current data regarding the prevalence of HUA in Chinese hypertensive patients are lacking. Our study aims to explore the prevalence and determinants of HUA in Chinese hypertensive adults.

Methods: Treatment-naive hypertensive adults or those taking single antihypertensive agent were included in a nationwide cross-sectional study. Basic demographics, antihypertensive medications, serum uric acid (UA), and other parameters were documented.

Results: The overall prevalence rate of HUA was 38.7% among 33,785 valid cases, 35.1% for males (UA >420 μmol/L), and 45.2% for females (UA >360 μmol/L). A multiple logistic regression analysis, adjusted for demographic and clinical factors (model 1), revealed that female sex [odds ratio (OR), 95% CI, 1.43, 1.36–1.51], age of ≥65 years (1.12, 1.05–1.19), low evaluated glomerular filtration rate [eGFR; 2.06, 1.91–2.23, the lowest [Q1] *vs.* the highest quartile (Q4)], unmarried (1.58, 1.10–2.27), Western China residency (3.21, 3.33–3.91), longer hypertension duration (1.97, 1.78–2.12, Q4 *vs.* Q1) and aspirin use (1.21, 1.14–1.29) were associated with HUA. In a multiple logistic regression analysis adjusted for clinical and metabolic parameters (model 2), female sex (OR, 95% CI, 1.34, 1.27–1.41), age of ≥65 years (1.09, 1.03–1.16), low eGFR (2.35, 2.19–2.52, Q1 *vs.* Q4), new–onset hypertension (2.01, 1.73–2.33), higher quartile of fasting blood glucose (FBG), triglyceride (TG), low density lipoprotein cholesterol (LDL-C) levels, and body mass index (BMI) were associated with higher risk of HUA (1.89, 1.76–2.03; 2.15, 1.99–2.31; 2.86, 2.67–3.06; 1.27, 1.27–1.36, respectively, Q4 *vs.* Q1). Losartan, valsartan, and nifedipine were associated with lower risk of HUA (OR, 95% CI, 0.77, 0.67–0.88, 0.68, 0.60–0.77; 0.87, 0.77–0.99, 0.79, 0.70–0.89 and 0.80, 0.70–0.91, 0.82, 0.72–0.92), respectively, in models 1 and 2.

Conclusions: The prevalence rate of HUA in Chinese hypertensive patients was 38.7%. Female sex, aging (≥65 years), and low eGFR were independent predictors of HUA. HUA was lower among the patients who were taking losartan, valsartan, and nifedipine. Western region residents, new-onset hypertension, longer hypertension duration, aspirin use, higher FBG, TG, LDL-C levels and BMI were potential risk factors for HUA.

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Introduction

Hypertension is one of the most important risk factors for cardiovascular diseases (CVDs), and is associated with metabolic disorders, including overweight/obesity, abnormal glucose and lipid profiles, as well as elevated blood uric acid (UA) level. Hyperuricemia (HUA) is usually defined as a serum UA level >420 μmol/L (7 mg/dL) for males and >360 μmol/L (6 mg/dL) for females (1). HUA induces the development of hypertension (2) and is associated with CVD mortality and all-cause mortality (3). Synergistic interactions between hypertension and HUA greatly increase the risks of subclinical atherosclerosis, CVDs, renal insufficiency and all-cause mortality (2,4,5). Therefore, screening and management of HUA in hypertensive patients should be valued.

Few systematic investigations have focused on the prevalence of HUA in the hypertensive population. A recent cross-sectional study in Africa demonstrated that the prevalence of HUA in newly diagnosed, untreated hypertensive patients was 46.9%, which was significantly higher than the 16.9% in normotensive individuals (6). A cross-sectional survey among a population aged 40–75 years in Xinyang, China, in 2007 showed that the prevalence rate of HUA in hypertensive patients was 14.1% in the rural area, and higher in males than in females (21.5% and 10.2%, respectively) (7). Big data on the prevalence of HUA in Chinese hypertensive patients are lacking. In addition, previous studies revealed that thiazide diuretics increased the serum UA level (8), while angiotensin II receptor blocker (ARB) losartan decreased the UA level to some degree (9,10), which indicated the contrasting effects of different antihypertensive agents on UA. However, these effects must be evaluated in a larger hypertensive population.

In view of this, the Chinese Cardiovascular Association and Chinese Society of Cardiology initiated the nationwide *Survey on Uric aCid in Chinese subjects with ESsential hypertenSion (SUCCESS)* study in multiple provinces and cities in June, 2018, aiming to reveal the prevalence and influential factors of HUA in hypertensive patients in the real world and provide reference for the management of HUA in this population in the future.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3458).

Methods

This was a cross-sectional study using a convenient sampling strategy to select subjects from a hospital-based population. From June to November 2018, hypertensive patients consecutively referred to the outpatient clinics of hospitals in 17 provinces and municipalities (Liaoning, Hebei, Henan, Shandong, Shanxi, Jiangsu, Anhui, Zhejiang, Hubei, Hunan, Fujian, Guangdong, Sichuan, Chongqing, Tianjin, Shanghai, and Beijing) across China were included in the survey. The subjects were required to meet the following criteria: (I) patients aged ≥18 years; (II) blood pressure (BP)-lowering treatment-naive hypertensive patients with BP of ≥140/90 mmHg, measured three times on different days, or those with established essential hypertension who had been taking a single antihypertensive medication regularly for at least 2 weeks; (III) patients who provided written informed consent before participation. Patients with hypertension comorbid with gout or those receiving urate-lowering therapy with xanthine oxidase inhibitors (XOIs), including allopurinol and febuxostat or uricosuric agents such as probenecid or benzbromarone were excluded from the survey.

In the survey, data from the participants were collected by uniformly trained physicians at each clinic, using a questionnaire included the following information: age, sex, educational level, marital status, history of smoking and/or drinking, history and duration of hypertension, use of antihypertensive agents and aspirin, and so on. Systolic BP, diastolic BP, heart rate, waist circumference (WC), and body mass index (BMI) were measured or calculated at the clinic. Fasting blood glucose (FBG), total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), blood creatinine, urea nitrogen, UA, and other parameters were obtained through biochemical tests routinely. Estimated glomerular filtration

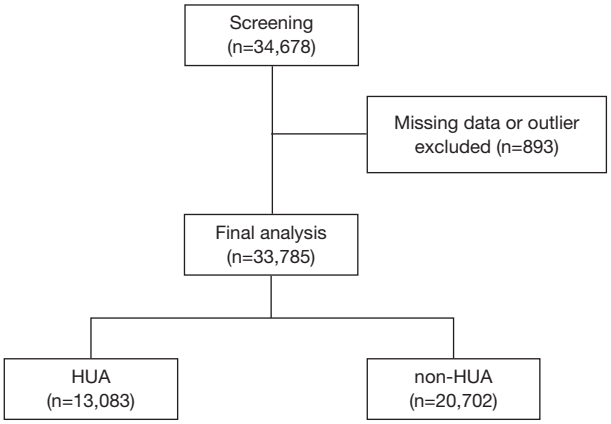

Figure 1 Flowchart of participants.

rate (eGFR) was calculated with the Cockcroft-Gault equation. The participants were divided into the HUA and non-HUA groups, referring to the definition of HUA as a serum UA level of >420 μmol/L for males or >360 μmol/L for females. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the central institutional review board of Peking University First Hospital (No. 2018-102). Written informed consent was obtained from all the participants.

Statistical analysis: Continuous variables were described as means ± standard deviation (SD) unless otherwise stated. Categorical variables were described as frequency or percentage. Missing data or outlier values were excluded from the analysis dataset. Chi-square or Fisher's exact tests, *t* tests, one-way analysis of variance (ANOVA) or nonparametric statistical methods were used for between-group parameter comparisons, including population characteristics and serum UA levels. Univariate and multivariate logistic regressions in separate models, adjusted for demographic, clinical and metabolic parameters and other possible confounders, were used to analyze the potential risk or protective factors for HUA. Subgroup population and sensitivity analyses for deferent parameters were also performed. P<0.05 was considered statistically significant. Statistical analyses were conducted using STATA 15.1 (College Station, Texas, USA).

Results

Baseline characteristics of the patients

A total of 34,678 patients were enrolled in the survey during the study period. Of them, 893 with missing data or outlier serum UA values (UA ≤0 or UA >1,000 μmol/L) were excluded and 33,785 were included in the statistical analyses (*Figure 1*). Among the patients included in the analyses, 21,777 (64.5%) were men. More than 90% of the patients had a history of hypertension and had been receiving a single antihypertensive medication. The median hypertension duration was around 5 years (range, 59–60 months), and the median antihypertensive medication duration was around 3 years (range, 35–38 months). More than 60% of the patients had high school education or lower, while 16.8% had an undergraduate degree or higher (*Table 1*).

Prevalence and gender differences of HUA

The prevalence rate of HUA was 38.7% in Chinese hypertensive population, 35.1% for males and 45.2% for females, as referring to the definition of HUA with serum UA level of >420 μmol/L for males or >360 μmol/L for females. The univariate analysis revealed that the risk of HUA increased by 53% in the females in comparison with that in the males [odds ratio (OR), 1.53; 95% CI, 1.46–1.60]. The multivariate logistic regression analysis, with adjustment for demographic and clinical parameters, including age, sex, marital status, educational level, region, eGFR, hypertension duration, antihypertensive medications, history of antihypertensive drug and aspirin use (model 1), revealed that the female hypertensive patients had a significantly higher risk of HUA than the males (OR, 1.43; 95% CI, 1.36–1.51) (*Table 2*).

Age and HUA

With age <65 years as control, the univariate logistic regression analysis revealed that age ≥65 years was a risk factor for HUA, with an increased relative risk of 32% (95% CI, 1.24–1.39). The multivariate logistic regression analysis revealed that age ≥65 years was still an independent risk factor for HUA even after adjustment for the above-mentioned confounders, with a 12% increased in relative risk (OR, 1.12; 95% CI, 1.05–1.19).

eGFR and HUA

When eGFR was categorized into quartiles (indicated by Q1, Q2, Q3 and Q4 from low to high) and the highest quartile (Q4) as control, the univariate analysis revealed

Table 1 Demograhic data and baseline characteristics

	HUA (N=13,083)	Non-HUA (N=20,702)	Statistics	P value
Age (years)	57.4 (11.0)	57.0 (10.8)	t=–3.17	0.002
Gender			χ^2=332.10	<0.001
Male	7,652 (58.5%)	14,125 (68.2%)		
Female	5,431 (41.5%)	6,577 (31.8%)		
Marital status			χ^2= 9.060	0.003
Single	99 (0.8%)	103 (0.5%)		
Married	12,984 (99.2%)	20,599 (99.5%)		
Region			χ^2=3,017.597	<0.001
Eastern	2,324 (17.8%)	7,711 (37.2%)		
Western	3,592 (27.4%)	2,164 (10.4%)		
Southern	4,313 (33.0%)	4,609 (22.3%)		
Northern	2,605 (19.9%)	5,979 (28.9%)		
Central	249 (1.9%)	239 (1.2%)		
Education levels			χ^2=35.045	<0.001
Junior high school	4,933 (37.7%)	7,946 (38.4%)		
Senior high school	3,558 (27.2%)	5,062 (24.5%)		
Junior college	2,491 (19.0%)	4,108 (19.8%)		
Undergraduate	1,703 (13.0%)	2,923 (4.1%)		
Postgraduate	398 (3.0%)	663 (3.2%)		
Previous hyertension			χ^2=57.379	<0.001
No	1,265 (9.7%)	1,520 (7.3%)		
Yes	11,818 (90.3%)	19,182 (92.7%)		
Duration of hyertension (month)	73.6 (59.6)	71.4 (58.8)	t=–3.14	0.002
Height (cm)	167.5 (7.9)	168.8 (7.6)	t=14.50	<0.001
Weight (kg)	69.3 (10.8)	69.7 (10.6)	t=3.63	<0.001
Waist circumference (cm)	82.4 (18.5)	85.4 (16.9)	t=15.46	<0.001
Body mass index (BMI)	24.6 (2.9)	24.4 (2.7)	t=–6.83	<0.001
UA (umol/L)	468.1 (66.5)	296.7 (78.2)	t=–215.31	<0.001
FBG (mmol/L)	5.8 (2.0)	5.3 (1.8)	t=–23.52	<0.001
TCHO (mmol/L)	4.7 (1.6)	4.3 (1.9)	t=–20.16	<0.001
TG (mmol/L)	1.9 (1.1)	1.7 (1.5)	t=–14.55	<0.001
LDL-C (mmol/L)	3.0 (2.2)	2.6 (1.3)	t=–19.92	<0.001
HDL-C (mmol/L)	1.7 (4.2)	1.7 (4.6)	t=0.66	0.506
SCr (umol/L)	91.5 (67.6)	82.0 (54.2)	t=–13.51	<0.001
BUN (mmol/L)	6.8 (18.5)	6.8 (17.0)	t=0.06	<0.951

Table 1 (*continued*)

Table 1 (*continued*)

	HUA (N=13,083)	Non-HUA (N=20,702)	Statistics	P value
ALT (IU/L)	32.9 (18.8)	28.9 (17.1)	t=–19.87	<0.001
AST (IU/L)	30.6 (21.6)	28.3 (21.2)	t=–9.37	<0.001
eGFR (C-G equation)	88.6 (37.2)	101.9 (43.9)	t=28.46	<0.001
Previous use of asirin			χ^2=38.331	<0.001
No	9,691 (74.1%)	15,947 (77.0%)		
Yes	3,392 (25.9%)	4,755 (23.0%)		
Antihyertensive agents			χ^2=140.29	<0.001
ACEIs	1,309 (10.0%)	1,999 (9.7%)		
ARBs	4,676 (35.8%)	8,544 (41.3%)		
CCBs	5,239 (40.1%)	7,659 (37.1%)		
β blockers	307 (2.35%)	594 (2.87%)		
Diuretics	153 (1.17%)	189 (0.91%)		
others	134 (1.02%)	193 (0.93%)		
none	1,258 (9.6%)	1,494 (7.2%)		
Duration of treatment (month)	41.3 (34.7)	46.1 (37.5)	t=11.12	<0.001

ACEIs, angiotensin converting enzyme inhibitors; ALT, asartate aminotransferase; ARBs, angiotensin recetor blockers; AST, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CCBs, calcium channel blockers; C-G equation, Cockcroft-Gault equation; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HDL-C, high density liorotein cholesterol; LDL-C, low density liorotein cholesterol; SCr, serum creatinine; TCHO, total cholesterol; TG, triglyceride; UA, uric acid.

that the ORs of HUA in Q1, Q2 and Q3 were 2.47 (95% CI, 2.32–2.63), 1.71 (1.61–1.83) and 1.28 (1.20–1.37), respectively. The multiple logistic regression analysis revealed that the ORs of HUA in Q1, Q2 and Q3 was 2.06 (1.91–2.23), 1.66 (1.54–1.79) and 1.246 (1.16–1.34), respectively. The lower the eGFR, the higher the risk of HUA.

Geographical differences in the prevalence of HUA

The prevalence rates of HUA in the five regions across China were 23.2%, 62.4%, 48.3%, 30.3% and 51.0% in the Eastern (Shandong, Jiangsu, Anhui, Zhejiang, and Shanghai), Western (Sichuan and Chongqing), Southern (Hunan, Fujian and Guangdong), Northern (Liaoning, Hebei, Shanxi, Tianjin, and Beijing), and Central regions (Henan and Hubei), respectively, lower in the Eastern region but higher in the Western region. With the Eastern region as control, the univariate analysis revealed that the risk of HUA progressively increased in the Northern, Southern, Central and Western regions, with 4.5-fold increase in the Western region (OR, 5.51; 95% CI, 5.13–5.91). The multiple logistic regression analysis revealed that the risk of HUA in the Western region was still the highest (OR, 3.60; 95% CI, 3.33–3.91).

HUA and educational levels

We found that the prevalence of HUA was 37.4% in the hypertensive patients with a college degree or higher (junior college graduates, undergraduates, and postgraduates, 12,286 cases) and 39.5% in those with a junior high school or high school degree (21,499 cases). With higher educational level (college degree or higher) as control, the univariate analysis revealed an increased risk of HUA in the hypertensive patients with relatively lower educational levels (junior high school or high school; OR, 1.09; 95% CI, 1.05–1.15). However, the multiple logistic regression analysis did not reveal a correlation between the prevalence of HUA and educational level (OR, 1.02; 95% CI, 0.96–1.07).

Table 2 Multivariate logistic regression analysis of the determinants of HUA in hypertensive patients

Factors	Model 1				Model 2			
	Beta	P value	OR	95% CI	Beta	P value	OR	95% CI
Female*#	0.359	0.000	1.432	1.358–1.510	0.292	0.000	1.339	1.271–1.411
Age ≥65 y*#	0.111	0.001	1.117	1.049–1.190	0.086	0.005	1.089	1.027–1.156
Unmarried**	0.457	0.013	1.579	1.100–2.269	0.242	0.136	1.274	0.927–1.752
Antihypertensive agents (others as control)								
Valsartan**#	–0.137	0.034	0.872	0.768–0.990	–0.236	0.000	0.790	0.701–0.890
Losartan*#	–0.264	0.000	0.768	0.672–0.878	–0.389	0.000	0.678	0.597–0.770
Nifedipine*#	–0.225	0.001	0.799	0.704–0.907	–0.203	0.001	0.816	0.724–0.920
β blockers*#	–0.335	0.001	0.716	0.592–0.866	–0.413	0.000	0.662	0.552–0.794
Use of Aspirin*	0.193	0.000	1.213	1.143–1.287	0.049	0.095	1.050	0.991–1.113
eGFR (quartiles *vs.* Q4)								
Q1*#	0.724	0.000	2.063	1.913–2.226	0.854	0.000	2.349	2.187–2.524
Q2*#	0.506	0.000	1.659	1.541–1.786	0.510	0.000	1.665	1.552–1.786
Q3*#	0.220	0.000	1.246	1.156–1.344	0.272	0.000	1.312	1.223–1.408
Regions (Eastern as control)								
Northern*	0.119	0.000	1.126	1.046–1.211	–			
Southern*	0.894	0.000	2.446	2.279–2.625				
Western*	1.282	0.000	3.604	3.326–3.906				
Central*	1.036	0.000	2.818	2.298–3.456				
Duration of antihypertensive therapy (quartiles compared with Q4)								
Q1*	0.626	0.000	1.869	1.713–2.040				
Q2*	0.415	0.000	1.514	1.392–1.647				
Q3*	0.331	0.000	1.392	1.289–1.504				
Duration of hypertension (quartiles *vs.* Q1)								
Q2*	0.527	0.000	1.694	1.555–1.845				
Q3*	0.535	0.000	1.707	1.567–1.860				
Q4*	0.676	0.000	1.966	1.780–2.172				
FBG (quartiles *vs.* Q1)								
Q2#					0.109	0.003	1.115	1.038–1.198
Q3#					0.591	0.000	1.807	1.682–1.940
Q4#					0.638	0.000	1.893	1.763–2.032
TG (quartiles *vs.* Q1)								
Q2#					0.418	0.000	1.518	1.409–1.636
Q3#					0.505	0.000	1.657	1.543–1.779
Q4#					0.763	0.000	2.145	1.988–2.314

Table 2 (*continued*)

Table 2 (*continued*)

Factors	Model 1				Model 2			
	Beta	P value	OR	95% CI	Beta	P value	OR	95% CI
LDL-C (quartiles *vs.* Q1)								
Q2#					0.365	0.000	1.440	1.341–1.547
Q3#					0.583	0.000	1.791	1.665–1.927
Q4#					1.050	0.000	2.857	2.666–3.062
BMI (quartiles *vs.* Q1)								
Q2					0.055	0.117	1.057	.986–1.133
Q3#					0.114	0.001	1.120	1.045–1.201
Q4#					0.236	0.000	1.266	1.181–1.358
New-onset hypertension#					0.695	0.000	2.005	1.728–2.326
Constant	–2.134	0.000	0.118		-2.428	0.000	0.088	

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; LDL-C, low density lipoprotein cholesterol; OR, odds ratio; TG, triglyceride. *, P<0.01; **, P<0.05, in model 1, adjustment of age, gender, marital status, education level, region, eGFR, duration of hypertension, history and application of antihypertensive drugs and aspirin; #, P<0.01, in model 2: adjustment of age, gender, marital status, eGFR, new-onset hypertension, antihypertensive drugs and aspirin application and metabolic parameters.

HUA and hypertension duration

The survey revealed that the hypertension duration was longer in the HUA group, than in the non-HUA group (mean, 73.6 months, *vs.* 71.4 months). When hypertension duration was divided into quartiles and with the lowest quartile (Q1) as control, the univariate analysis revealed that the ORs of HUA in Q2, Q3 and Q4 were 1.26 (95% CI, 1.18–1.34), 0.98 (0.92–1.05), and 1.14 (1.07–1.22), respectively. The multiple logistic regression analysis revealed that the ORs of HUA in Q2, Q3, and Q4 were 1.69 (95% CI, 1.56–1.85), 1.71 (1.57–1.86), and 1.97 (1.78–2.12), respectively. The longer the hypertension duration, the higher the risk of HUA.

HUA and antihypertensive medication

The results showed that BP-lowering treatment-naive hypertensive patients accounted for 8.1% (2,752 cases) of the total population and those with established hypertension who had been receiving a single antihypertensive drug accounted for 91.7% (30,996 cases), most of whom had been receiving ARBs (39.1%, 13,220/33,785), calcium channel blockers (CCBs; 38.2%, 12,898/33,785) or angiotensin converting enzyme inhibitors (ACEIs; 9.8%, 3,308/33,785) and few had been taking β-blockers (2.7%, 901/33,785), diuretics (1.0%, 342/33,785) or other antihypertensive drugs (0.9%, 327/33,785). With BP-lowering treatment naivety as control, the univariate analysis revealed that the use of ARBs, ACEIs, CCBs and β-blockers was associated with decreased risk of HUA in the hypertensive patients. The corresponding ORs were 0.65 (95% CI, 0.60–0.71), 0.78 (0.70–0.86), 0.81 (0.75–0.88), and 0.61 (0.53–0.72), respectively. The ORs for diuretics and other antihypertensive drugs were 0.96 (95% CI, 0.77–1.21) and 0.83 (0.65–1.04), which were not statistically significant. Further analysis revealed that the top four most frequently used antihypertensive agents were valsartan (7,808 cases), nifedipine (controlled-release formulation; 7,341 cases), amlodipine (5,134 cases), and losartan (4,559 cases). The univariate analysis revealed that the use of losartan, valsartan and nifedipine correlated with lower risk of HUA. The corresponding ORs were 0.58 (95% CI, 0.53–0.64), 0.68 (0.62–0.74), and 0.73 (0.67–0.80), respectively. By contrast, amlodipine had no such an effect, with an OR of 0.95 (95% CI, 0.87–1.05). With other antihypertensive drugs as control, the multivariate logistic regression analysis revealed that only losartan, valsartan, nifedipine and β-blockers were associated with lower risk of HUA. The ORs were 0.77 (95% CI, 0.67–0.88), 0.87 (0.77–0.99), 0.80 (0.70–0.91), and 0.72 (0.59–0.87), respectively. ACEI no

longer showed a protective effect for HUA, with an OR of 0.97 (95% CI, 0.85–1.12). Amlodipine and diuretics non-significantly increased the risk of HUA, with ORs of 1.09 (95% CI, 0.96–1.24) and 1.05 (0.81–1.35) respectively. When dummy variables were used in the regression analysis, the multivariate logistic regression analysis indicated that medication with losartan, valsartan and nifedipine, and β-blockers significantly reduced the risk of HUA, with ORs of 0.68 (95% CI, 0.60–0.77), 0.79 (0.70–0.89), 0.82 (0.72–0.92), and 0.66 (0.55–0.79), respectively, P≤0.001), as compared with nonuse of these drugs. ACEI marginally reduced the occurrence of HUA (OR, 0.87; 95% CI, 0.76–0.99; P=0.04), whereas amlodipine and diuretics non-significantly increased the risk of HUA (OR, 1.06, 95% CI, 0.93–1.19 and OR, 1.12, 95% CI, 0.87–1.43, respectively, P=0.39).

HUA and antihypertensive therapy duration

When the antihypertensive therapy durations were divided into quartiles, with the highest quartile (Q4) as control, the univariate analysis revealed that the ORs of HUA in Q1, Q2, and Q3 were 0.84 (95% CI, 0.78–0.89), 1.24 (1.16–1.32), and 0.95 (0.90–1.01), respectively. The multiple logistic regression analysis revealed that short antihypertensive therapy duration was correlated with high risk of HUA [ORs (95% CI) in Q1, Q2 and Q3 were 1.87 (1.71–2.0), 1.51 (1.39–1.65) and 1.39 (1.29–1.50), respectively, in contrasted to Q4].

HUA and aspirin use

Of the hypertensive patients who had been taking aspirin regularly (8,147 cases), 41.6% presented with HUA, whereas of the aspirin-naive patients (25,638 cases), 37.8% had HUA. With aspirin naivety as control, the univariate analysis revealed that the use of aspirin increased the risk of HUA (OR, 1.19; 95% CI, 1.13–1.26). The multiple logistic regression analysis revealed that aspirin use was a predictor of HUA, and the relative risk increased by 21% (OR, 1.21; 95% CI, 1.14–1.29).

HUA and other metabolic parameters

The mean (± SD) and median serum UA levels were respectively 468.1 (±66.5) μmol/L and 456.7 μmol/L in the HUA group, and 296.7 (±78.2) μmol/L and 312 μmol/L in the non-HUA group, respectively. The univariate analysis revealed that HUA was correlated with blood glucose level, lipid profile, and other metabolic parameters. With the increasing quartiles of fasting glucose, TG, and LDL-C levels, and BMIs from Q1 to Q2 to Q3 to Q4, the risk of HUA also increased. The multivariate logistic regression analysis revealed that after adjustment for the clinical and metabolic factors (model 2), including age, sex, marital status, eGFR, new-onset hypertension, antihypertensive drugs and aspirin use, higher levels of fasting glucose, TG, LDL-C and BMI were still associated with higher risk of HUA (*Table 2*).

HUA and new-onset hypertension

The survey showed that the prevalence of HUA in patients with new-onset hypertension (2,785 cases) was up to 45.4%, higher than that in those with an established hypertension (38.1%, 31,000 cases). With the patients with established hypertension as control, the univariate analysis revealed that the relative risk of HUA increased by 35% in the patients with new-onset hypertension (OR, 1.35; 95% CI, 1.25–1.46). The multivariate logistic regression analysis (model 2) revealed that after adjustment for the clinical and metabolic parameters, new-onset hypertension was still a risk factor for HUA (OR, 2.01; 95% CI, 1.73–2.33).

In addition, the data showed that the prevalence of HUA in the unmarried hypertensive patients was 49%, higher than the 39% in those who were married. The univariate analysis revealed that singlehood increased the risk of HUA (OR, 1.53; 95% CI, 1.06–2.01). Compared with those who were married, unmarried hypertensive patients had a 58% increased risk of HUA (OR, 1.58; 95% CI, 1.10–2.27) in the multivariate logistic regression analysis (model 1), but the risk of HUA was not significant after the inclusion of metabolic parameters (OR, 1.27; 95% CI, 0.93–1.27; model 2). Despite that the use of aspirin was associated with the increased risk of HUA in model 1, it was not significant as the metabolic parameters were included in model 2. Female sex, age of ≥65 years, and lower eGFR were independently associated with higher risk of HUA, while use of losartan, valsartan, and nifedipine were associated with lower risk of HUA, with similar results between models 1 and 2 (*Table 2*).

Discussion

UA is the ultimate catabolite of purine metabolism in humans and higher primates. HUA is related to the

occurrence and development of hypertension. Previous studies found that 47% of the hypertensive population had HUA (11). Epidemiological studies have confirmed that HUA has a strong correlation with the occurrence of hypertension. Pooled analysis revealed that for every 1mg/dL increase in serum UA, the risk of hypertension increased by 13%, and this effect was more pronounced in women and young adults (12). An experimental study showed that UA increases BP at the initial stage, in a UA-dependent manner, and that BP could be reduced with UA-lowering medications; however, prolonged HUA results in irreversible sodium-sensitive hypertension that becomes UA independent (13,14). The early stage (UA causes rapid increase in BP) mainly involves an increase in renin activity and a reduction in circulating nitrates, which results in vasoconstriction that can be reversed by administration of UA-lowering agents or RAS inhibitors (15,16). The late and long-term mechanism of high BP may be associated with renal interstitial vascular structural changes. Studies have revealed that UA enters vascular smooth muscle cells (VSMCs) via UA anion transporter-1 channels, which leads to the activation of kinases, nuclear transcription factors, cyclooxygenase 2, platelet-derived growth factor and inflammatory protein (e.g., C-reactive protein and monocyte chemoattractant protein 1), which eventually results in VSMCs proliferation, shifted pressure natriuresis and sodium-sensitive hypertension (17-19). Other studies have found that HUA is associated with increased CVD risk (3-5). Recent genetic evidences based on conventional and novel Mendelian randomization approaches suggest a modest, if any, causal effect of plasma UA concentration on the development of CVDs (20,21). Despite these evidences, the association between serum UA and CVDs is currently considered to be not always independent of traditional risk factors or diseases, such as hypertension, diabetes, or chronic kidney diseases (12).

A previous study demonstrated that the prevalence of HUA in hypertensive patients in a rural area (Xinyang) in China was approximately 14% (7). In this survey, HUA was found in approximately two-fifth of hypertensive patients. The major difference might reflect the transition of the lifestyle and dietary structure of the residents in China. Increasing intake of the high-calorie diet with meat, fruit juice, or other fructose-rich drinks and foods is related to the development of HUA.

The occurrence of HUA in hypertensive patients is affected by many factors. Aging was an independent predictor of HUA, and the risk of HUA increased in the hypertensive patients aged ≥65 years in the survey. Compared with the males, the female hypertensive patients had a significant increase in the risk of HUA, which may be due to the elevated serum UA level in the postmenopausal period (22). Excretion of urate decreased with impaired renal filtration, as the survey demonstrated that lower eGFR was associated independently with higher risk of HUA. The study also found that the prevalence of HUA in the residents of Western China was significantly higher than that in the residents of the Eastern region, which may be related to the dietary structure and habits of the residents in these regions. The Western residents had the tendency to have a higher intake of purine-rich meat, while the Eastern residents had a relatively lighter diet. In addition, longer hypertension duration, lower educational level (high school or lower), singlehood, metabolic disorders (e.g., impaired glucose tolerance/diabetes, dyslipidemia, and obesity), and aspirin use are potential risk factors for HUA in separate models adjusted for demographic and clinical confounders. These factors identified in the survey are routinely collected in clinical practice and may be readily incorporated into risk prediction. In this study, the univariate and multivariate regression analyses both revealed that singlehood was a predictive factor for HUA, which may be explained by the fact that most of the unmarried patients were younger, had intemperate diet, or had other risk factors. However, the result should be interpreted cautiously, as the proportion of unmarried people in the survey was <1% (only 202 cases), and bias could not be excluded. In addition, the present study showed that the prevalence of HUA in the patients with new-onset hypertension was higher than in those with established hypertension. However, owing to the small number of patients in this group (2,570 cases), this finding should also be interpreted with caution.

Moreover, for hypertensive patients receiving antihypertensive medications, the class of drugs can be associated with HUA occurrence. A study of data from the UK general practice database showed that different antihypertensive drugs had different effects on HUA-derived gout. CCBs and losartan had an attenuating effect on gout, whereas diuretics, β blockers, ACEIs and other non-losartan ARBs increased the risk of gout. Further analysis indicated that the attenuating effect of CCBs on gout was time dependent; that is, CCBs slightly increased the risk of gout in the first year, but decreased it gradually thereafter on a yearly basis. The effect of losartan was also time dependent, showing a continuously decreasing trend (23). A community study (ARIC) in the United States

suggested that non-diuretic antihypertensive medications significantly reduced the incidence of gout in hypertensive patients, as compared with untreated patients, with an adjusted hazard ratio (HR) of 0.64 (95% CI, 0.49–0.86). Compared with non-diuretics, diuretics (either thiazide, or loop diuretics) significantly increased the risk of gout (HR, 1.48; 95% CI, 1.11–1.98). Compared with non-thiazide diuretics, thiazides increased risk of gout (HR, 1.44; 95% CI, 1.00–2.01). Use of loop diuretics also demonstrated a significant increase in the risk of gout, as compared with the use of non-loop diuretics (HR, 2.31; 95% CI, 1.36–3.91) (8). A study on a hypertensive population in Taiwan found that use of diuretics and β blockers could predict HUA, while the use of ACEIs, CCBs and ARBs had little relationship with the occurrence of HUA (24). A study in Japan showed that administration of diuretics, β-blockers, and α-blockers increased serum UA levels in hypertensive patients, while use of CCBs, ACEIs, ARBs, including losartan did not increase UA levels (25). In our investigation, we found that the use of antihypertensive agents, including ARBs, ACEIs, CCBs or β blockers, was associated with a lower risk of HUA compared with no treatment for hypertension. Further analysis revealed that losartan, valsartan, nifedipine and β-blockers were protective factors for HUA, with lower risk of HUA in the patients who were taking these medications. Other antihypertensive drugs including amlodipine and diuretics did not significantly increase the risk of HUA. Previous literature showed that losartan, an ARB, could promote UA excretion, thereby reducing UA levels (9,10). Except for losartan, other ARBs did not show definite UA-lowering effects (26). Controlled-release nifedipine was also found to be effective for reducing serum UA levels in patients with coronary heart disease in the ACTION trial (27), and the uricosuric effect was confirmed in the urate under-excretion mice model (28). The findings of this study are generally in consistent with the results of previous studies. However, the protective effect of β-blockers for HUA should be interpreted with caution. First, only few patients in this study took β blockers, accounting for only 2.7% of the total population; thus, the findings may be biased. Second, metoprolol and atenolol have been reported to increase UA levels (29,30), while celiprolol, a vasodilating β-blocker, has a tendency to reduce UA levels slightly (31). Moreover, this investigation found that diuretics showed a tendency to increase the risk of HUA, but it was not statistically significant, which may be due to the low proportion and quantity of patients who were taking diuretics, and the low statistical power.

Our study has several limitations. Owing to its cross-sectional design, we could not analyze the effects of the dynamic changes of the metabolic parameters such as glucose or lipid profiles, as well as the antihypertensive agents on HUA. To avoid affecting the result of the HUA prevalence, we excluded patients with hypertension comorbid with gout or those who had been taking urate-lowering therapeutic medications, including allopurinol, febuxostat or benzbromarone, etc. from the survey. While losartan, with the uricosuric potential, might still have a modest impact on the result. As we exclude the patients who had been taking losartan, and recalculate the data, the prevalence of HUA will be 1% higher than the 38.7% in the overall population. Although we included demographic or clinical parameters in the different models in the logistic regression analysis, some factors with predictive potential might have been neglected. As aforementioned, some bias could exist owing to the small proportion or number of the patients under the different categories. In addition, as this study included only Chinese patients with hypertension, the results of the survey should not be extrapolated to other ethnicities.

Conclusions

This large-sample population survey showed that the prevalence of HUA in Chinese hypertensive patients was 38.7%. Female sex, aging (≥65 years) and low eGFR were independent risk factors for HUA. The prevalence of HUA was lower among the patients who were taking losartan, valsartan and nifedipine. Western region residents, new-onset hypertension, longer hypertension duration, aspirin use, and higher FBG, TG, and LDL-C levels and BMI might be associated with increased risk of HUA.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was in accordance with the Declaration of Helsinki (as revised in 2013). The protocol was approved by the central institutional review board of Peking University First Hospital (No. 2018-102). Written informed consent was obtained from all participants.

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