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Association between serum uric acid-to-high-density lipoprotein cholesterol ratio and insulin resistance in patients with type 2 diabetes mellitus

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Keywords
High density lipoprotein cholesterol, Uric acid, Uric acid-to-high-density lipoprotein cholesterol ratio

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ABSTRACT

Introduction: Previous studies have shown that the serum uric acid-to-high-density lipoprotein cholesterol ratio (UHR) is related to metabolic syndrome. However, no existing study has examined the relationship between UHR and insulin resistance (IR). Therefore, this study aims to explore the association between the UHR and IR in patients with type 2 diabetes mellitus (T2DM).

Methods: Patients with type 2 diabetes mellitus (1,532 males and 1,013 females) were enrolled. Insulin resistance was measured by homeostatic model assessment of insulin resistance (HOMA-IR) and was defined as HOMI-IR ≥ 2.69. Pearson correlation, multiple logistic regression, ROC analysis, and subgroup analysis were used to evaluate the association between UHR and IR.

Results: UHR was associated with HOMA-IR in patients with type 2 diabetes mellitus (pearson's correlation coefficient = 0.274 in males and 0.337 in females, $P < 0.001$). Multiple logistic regression analysis showed that UHR was significantly correlated with insulin resistance (OR = 1.06, 95%CI = 1.03–1.08 in males and OR = 1.11, 95%CI = 1.08–1.15 in females). The area under the ROC curve (AUC) of UHR (AUC = 0.665 for males and 0.717 for females, all $P < 0.01$) was the largest compared with that of UA and HDL-C in insulin resistance. Subgroup analysis showed that there was a more significantly positive correlation among subjects with BMI ≥ 24 kg/m^2, age < 60 years old, HbA1c < 7%, non-hypertension, or in female subjects.

Conclusion: Elevated UHR is significantly correlated with insulin resistance, which can be used as an indicator of insulin resistance in patients with type 2 diabetes mellitus.

INTRODUCTION

Insulin resistance (IR) is regarded as a significant factor in various pathological conditions, such as atherosclerosis, metabolic syndrome (MetS), diabetes mellitus, and hypertension. Therefore, it is crucial to accurately measure insulin resistance. The gold standard for insulin resistance measurement is the hyperinsulinemic-euglycemic clamp[1], but it is not suitable for routine clinical use due to accessibility, cost, replicability, and reproducibility issues[1–5]. As an alternative, the homeostasis model assessment for insulin resistance (HOMA-IR) index is used widely in adults[6]. However, HOMA calculations require the measurement of fasting plasma insulin, which is not done routinely in clinical settings. Therefore, there is a need for a diagnostic test that is precise, easy, and cost-effective in predicting insulin resistance.

Uric acid can cause atherosclerosis and insulin resistance by reducing nitric oxide production, promoting vascular smooth muscle proliferation, and resulting in endothelial dysfunction[7]. Additionally, low levels of HDL-C play a role in the development of metabolic syndrome and insulin resistance[8–12]. More recently, the uric acid-to-HDL ratio (UHR) has been identified as a marker that increases in inflammatory conditions[13]. Kocak *et al.*

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(2019) proposed the use of UHR as an effective diagnostic tool for identifying metabolic syndrome in individuals with type 2 diabetes[14]. Furthermore, UHR has been found to be significantly correlated with fasting plasma glucose and HbA1c levels, making it a useful marker for assessing the control of type 2 diabetes mellitus in males[15], as well as in hepatic steatosis[16], non-alcoholic fatty liver disease[17], and Hashimoto's thyroiditis[13].

Despite the findings outlined above, the association between the UHA and insulin resistance in patients with type 2 diabetes mellitus remains unclear. In this study, a large cross-sectional study was conducted to investigate the association between UHR and insulin resistance and to determine whether UHR could serve as a practical and novel biomarker for diagnosing insulin resistance.

METHODS

Subjects and study design

In this cross-sectional study, a total of 2,545 patients with type 2 diabetes mellitus who were admitted to the Department of Endocrinology of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University between January 2020 and August 2022 were included. The study was approved by the hospital's ethical review committee (approval number: LCKY2020-01), and written consent was obtained from all patients with type 2 diabetes mellitus. The inclusion criteria were as follows: a diagnosis of type 2 diabetes mellitus according to WHO criteria, age ≥ 20 years old, complete biochemical parameters, and clinical data. Patients with an alcohol intake of 70 g/week or more (females) and 140 g/week or more (males), severe kidney dysfunction, other infectious or systemic diseases, and those who underwent uric acid-reducing therapy were excluded.

Biochemical and anthropometric measurements

The following data were collected at admission: history of hypertension, smoking habits, alcohol intake, application of lipid-lowering drugs (LLDs), and physical measurements including height, blood pressure, waist circumference, and weight. Specifically, the definitions of alcohol status, hypertension, BMI, and smoking were described in our previous study[18].

Blood samples were collected after overnight fasting and 2 h after breakfast on the second day of admission. Low-density lipoprotein cholesterol (LDL-C), glycosylated hemoglobin (HbA1c), serum uric acid (UA), total cholesterol (TC), fasting C-peptide (FCP), triglycerides (TG), albumin, 2 h postprandial C-peptide (2 h PCP), alanine aminotransferase (ALT), creatinine, high-density lipoprotein cholesterol (HDL-C), aspartate transaminase (AST), 2 h postprandial plasma glucose (2 h PPG) and fasting plasma glucose (FPG) were determined as described previously[18].

Assessment of IR

Insulin resistance was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR) formula: HOMA-IR = 1.5 + FPG [mmol/L] × FCP [pmol/L]/2,800[19]. Insulin resistance was defined as HOMI-IR ≥ 2.69[20].

Statistical analysis

UHR (%) was calculated by UA (mg/dL)/HDL (mg/dL) *100. The data were analyzed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The UA, HDL, and UHR were different between genders; as a result, males and females were analyzed independently. The normality of continuous variables was assessed, and were expressed as median and interquartile range or mean ± SD. In order to assess the distinctions between the two groups, the Mann–Whitney *U* test or the *t*-test were adopted for continuous variables, and chi-square tests were adopted for categorical variables. In addition, Pearson correlation was utilized to examine the associations between UHR and metabolic risk factors. The patients were divided into quartiles based on their UHA levels (≤8.95, 8.95–12.59, 12.59–16.90, ≥16.90 in the female group, ≤12.56, 12.56–16.70, 16.70–22.09, ≥22.09 in the male group). Subgroup analysis was used to stratify the patients according to gender, age, BMI, HbA1c levels, and hypertension. Binary logistic regression was used to assess the association between UHA levels, quartiles, and the presence of insulin resistance. Receiver operating characteristic (ROC) curve analysis was carried out to assess the diagnostic effectiveness of UHR in detecting IR. $P < 0.05$ was considered as a significant difference.

RESULTS

Characteristics of participants with IR and non-IR

As presented in Table 1, the prevalence of insulin resistance reached 15.9% in males and 17.5% in females, respectively. The HOMA-IR, proportion individuals with hypertension, the percentages of the subjects taking LLD, weight, WC, SBP, HbA1c, FPG, FCP, 2 h PCP, creatinine, uric acid, TG, and UHR levels were all higher in patients with IR than in individuals without IR for both genders ($P < 0.001$). Female subjects with insulin resistance were older than non-IR subjects ($P < 0.001$). Furthermore, LDL levels were lower in patients with insulin resistance than in individuals without insulin resistance for both genders.

Correlation between UHR and clinical and biochemical parameters

Pearson's correlation of UHR with the metabolic parameters can be found in Table 2. It could be observed that in males, UHR was positively correlated with BMI ($r = 0.247$, $P < 0.001$), WC ($r = 0.199$, $P < 0.001$), SBP ($r = 0.046$, $P = 0.050$), DBP ($r = 0.088$, $P < 0.001$), TG ($r = 0.408$, $P < 0.001$), FPG ($r = 0.067$, $P = 0.009$), and FCP ($r = 0.277$, $P < 0.001$). In females, BMI ($r = 0.0.174$, $P < 0.001$), WC ($r = 0.190$, $P < 0.001$), SBP ($r = 0.057$, $P = 0.043$), DBP ($r = 0.091$, $P = 0.001$), HbA1c ($r = -0.072$, $P = 0.020$), TG ($r = 0.398$, $P < 0.001$), FPG ($r = 0.094$, $P = 0.003$), FCP ($r = 0.373$, $P < 0.001$) were correlated with UHR (Table 2).

Table 1 | Baseline characteristics of the patients with type 2 diabetes mellitus stratified by insulin resistance and gender

	Male		*P*-value	Female		*P*-value
	IR positive	IR negative		IR positive	IR negative	
N	244	1,288		177	836	
Age, years	55.3 ± 16.5	55.7 ± 14.1	0.737	66.5 ± 13.8	61.8 ± 13.6	<0.001
Duration of diabetes, year	4.5 ± 5.9	5.3 ± 6.2	0.483	7.5 ± 6.2	9.0 ± 6.5	0.285
Hypertension, *n* (%)	60.1	42.3	<0.001	65.5	50.1	0.004
Height, cm	169.7 ± 6.2	169.0 ± 7.8	0.167	156.1 ± 5.9	156.6 ± 7.7	0.439
Weight, cm	76.4 ± 18.1	69.1 ± 12.7	<0.001	61.9 ± 12.2	58.1 ± 12.0	<0.001
Body mass index, kg/m^2	26.3 ± 5.2	24.4 ± 11.2	0.013	25.3 ± 4.4	24.0 ± 9.9	0.096
Waist circumference, cm	92.9 ± 12.7	88.1 ± 22.9	<0.001	88.3 ± 10.1	84.5 ± 11.1	<0.001
Systolic blood pressure, mmHg	147.0 ± 23.7	138.5 ± 26.5	<0.001	149.0 ± 25.8	142.6 ± 27.8	0.005
Diastolic blood pressure, mmHg	87.3 ± 7.3	84.1 ± 24.9	0.045	82.5 ± 7.9	82.0 ± 7.9	0.407
Current smoking, %	40.2	41.8	1.000	0	1.3	0.601
Current drinking, %	11.3	10.2	0.726	1.8	0	0.504
Hemoglobin A1c, mmol/L	8.8 ± 2.1	9.5 ± 2.3	<0.001	8.6 ± 1.7	9.4 ± 2.2	<0.001
FPG, mmol/L	8.1 ± 2.4	6.3 ± 1.7	<0.001	8.4 ± 2.2	6.7 ± 1.9	<0.001
2 h PPG, mmol/L	16.1 ± 3.8	16.3 ± 3.8	0.357	17.1 ± 4.0	17.2 ± 3.9	0.744
FCP, ng/mL	2.04 ± 0.98	0.66 ± 0.37	<0.001	1.96 ± 0.76	0.65 ± 0.37	<0.001
2 h PCP, ng/mL	4.67 ± 2.58	2.54 ± 1.84	<0.001	4.78 ± 2.69	2.41 ± 1.79	<0.001
HOMA-IR	3.45 ± 1.43	2.00 ± 0.29	<0.001	3.37 ± 0.72	2.02 ± 0.30	<0.001
Albumin, g/dL	40.9 ± 5.4	40.4 ± 4.2	0.144	41.3 ± 6.13	39.7 ± 3.74	<0.001
Creatinine, μmol/L	102.0 ± 76.9	75.3 ± 28.7	<0.001	74.1 ± 40.9	58.2 ± 33.7	<0.001
Uric acid, μmol/L	421.9 ± 122.1	358.6 ± 101.6	<0.001	376.4 ± 121.6	300.8 ± 92.1	<0.001
Total cholesterol, mmol/L	4.52 ± 1.48	4.49 ± 1.29	0.712	4.52 ± 1.32	4.64 ± 1.20	0.262
Triglycerides, mmol/L	2.88 ± 3.21	1.88 ± 1.71	<0.001	2.53 ± 1.87	1.72 ± 1.13	<0.001
HDL-cholesterol, mmol/L	0.93 ± 0.30	0.99 ± 0.29	0.003	1.00 ± 0.30	1.14 ± 0.31	<0.001
LDL-cholesterol, mmol/L	2.57 ± 1.02	2.82 ± 1.08	0.001	2.61 ± 1.13	2.87 ± 1.05	0.005
UHR (%)	21.7 ± 8.8	17.4 ± 7.5	<0.001	17.9 ± 7.9	12.7 ± 6.0	<0.001

Values are mean ± SD or number (%). $P < 0.05$ was deemed significant (comparison between IR positive and IR negative). 2 h PPG, 2 h postprandial plasma glucose; BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; LLD, lipid-lowering drugs; TC, total cholesterol; TG, triglyceride; UHR, serum uric acid-to-high-density lipoprotein cholesterol ratio.

Table 2 | Pearson correlation of UHR levels with clinical and biochemical parameters

Variable	Male		Female	
	r	*P*	*r*	*P*
BMI	0.247	<0.001	0.174	<0.001
WC	0.199	<0.001	0.190	<0.001
SBP	0.046	0.050	0.057	0.043
DBP	0.088	<0.001	0.091	0.001
HbA1c	0.017	0.524	−0.072	0.020
TG	0.408	<0.001	0.398	<0.001
LDL-C	−0.123	<0.001	−0.194	<0.001
FPG	0.067	0.009	0.094	0.003
FCP	0.277	<0.001	0.373	<0.001

Correlation between UHA and IR

The level of UHR was significantly positively correlated with the HOMA-IR level ($r = 0.274$, $P < 0.001$ in males, $r = 0.337$, $P < 0.001$ in females; Figure 1). Table 3 shows binary logistic analysis for the association between UHA with insulin resistance in patients with type 2 diabetes mellitus. Before (Model 1) and after adjustment for age, BMI (Model 2), a higher UHA level was associated with an increased risk of insulin resistance ($P < 0.001$). After further correction for LLDs, BMI, WC, SBP, DBP, HbA1c, serum creatinine, serum albumin, UHR, drinking, and smoking (Model 3), the UHA level continued to be positively correlated with the presence of insulin resistance regardless of gender (all $P < 0.001$).

Subgroup analysis to assess the relationship between UHR and insulin resistance

In order to evaluate the effects of subgroups in modifying the association between UHR and insulin resistance, subgroup analyses were used by age (<60 or 60 years old), BMI (<24 or ≥ 24 kg/m^2), HbA1c (<7% or ≥7%), and history of hypertension (Figure 2). It was found that the *P* values for the subgroups were less than 0.005. UHR was independently

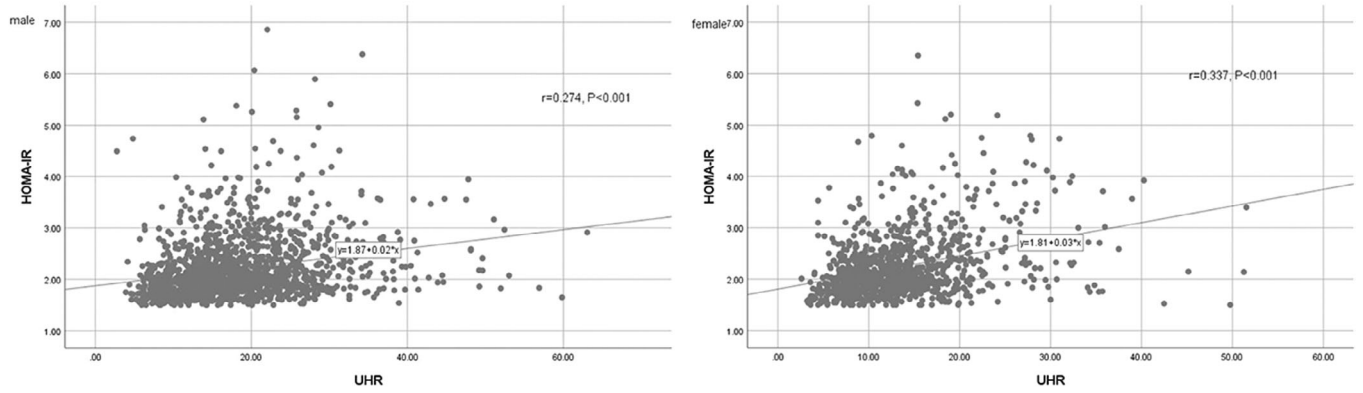

Figure 1 | Scatter diagrams showing the correlation between the UHR and HOMA-IR.

Table 3 | Association of the insulin resistance with UHR levels

	Crude model		Model I		Model II	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Male						
UHR	1.06 (1.05–1.08)	<0.001	1.06 (1.05–1.08)	<0.001	1.06 (1.03–1.08)	<0.001
UHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	1.53 (0.94–2.49)	0.088	1.52 (0.93–2.49)	0.096	1.43 (0.79–2.57)	0.236
Q3	2.48 (1.57–3.90)	<0.001	2.49 (1.58–3.94)	<0.001	2.46 (1.43–4.25)	0.001
Q4	4.14 (2.68–6.41)	<0.001	4.19 (2.70–6.52)	<0.001	3.64 (2.12–6.25)	<0.001
Female						
UHR	1.11 (1.08–1.14)	<0.001	1.11 (1.08–1.14)	<0.001	1.11(1.08–1.15)	<0.001
UHR (quartile)						
Q1	Ref		Ref		Ref	
Q2	1.00 (0.52–1.91)	1.000	1.00 (0.52–1.92)	1.000	0.79 (0.37–1.65)	0.523
Q3	2.99 (1.73–5.17)	<0.001	2.90 (1.66–5.05)	<0.001	2.27 (1.20–4.28)	0.011
Q4	6.40 (3.77–10.84)	<0.001	6.43 (3.75–11.02)	<0.001	4.16 (2.20–7.88)	<0.001

Crude model: adjusted for none. Model I: adjusted for age and BMI. Model II: adjusted for age, BMI, DD, WC, SBP, DBP, HbA1c, serum creatinine, serum albumin, UHR, drinking, smoking.

correlated with insulin resistance, and this independent association was more obvious in patients with type 2 diabetes mellitus with a BMI ≥ 24 kg/m^2, age < 60 years old, HbA1c < 7%, and no hypertension.

The predictive value of UHR for IR

The receiver operating characteristic curve (ROC) of UHR, UA, and HDL-C to diagnosing insulin resistance is illustrated in Figure 3. Table 4 shows that the area under the curve (AUC) for UHR in the ROC analysis was 0.665 (95% CI: 0.627–0.703) in males, 0.717 (95% CI: 0.674–0.760) in females, which was considerably higher than that of UA and HDL-C ($P < 0.001$), suggesting that UHR may be a better indicator for insulin resistance than just UA or HDL-C alone, although its diagnostic accuracy is still somewhat limited.

DISCUSSION

Our study provides strong evidence that UHR is positively correlated with an increase in HOMA-IR and the risk of insulin resistance (IR) in a mass of patients with type 2 diabetes mellitus. This relationship remains consistent regardless of gender, BMI, age, HbA1c, and history of hypertension. Notably, our ROC analysis demonstrates that UHR is more effective in detecting insulin resistance compared with UA or HDL-C alone, indicating that UHR is a specific and sensitive marker for insulin resistance.

Recent prospective studies in an adult population have shown that hyperuricemia is a predictor of insulin resistance and type 2 diabetes mellitus[21–23]. After a 15-year follow-up, Krishnan *et al.*[22] found that hyperuricemia increases the risk of developing type 2 diabetes mellitus by 1.87-times and insulin

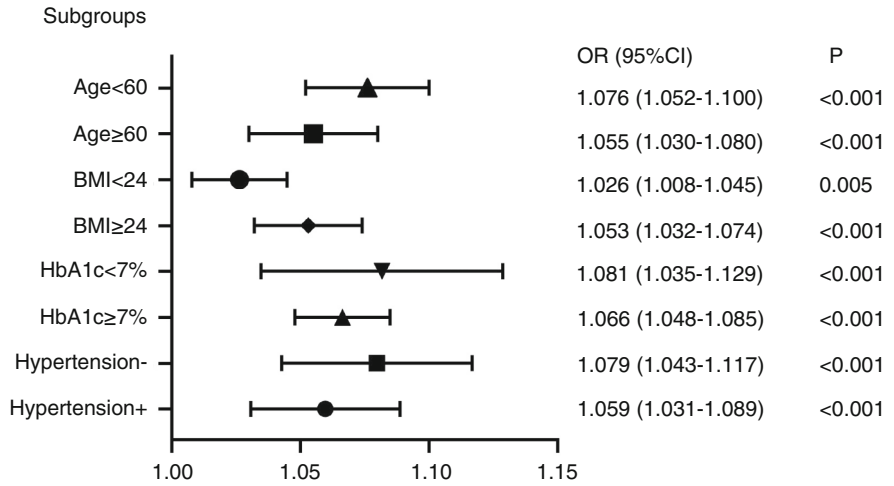

Figure 2 | Subgroup analysis based on the multivariate logistic regression analysis of the association between UHR and insulin resistance.

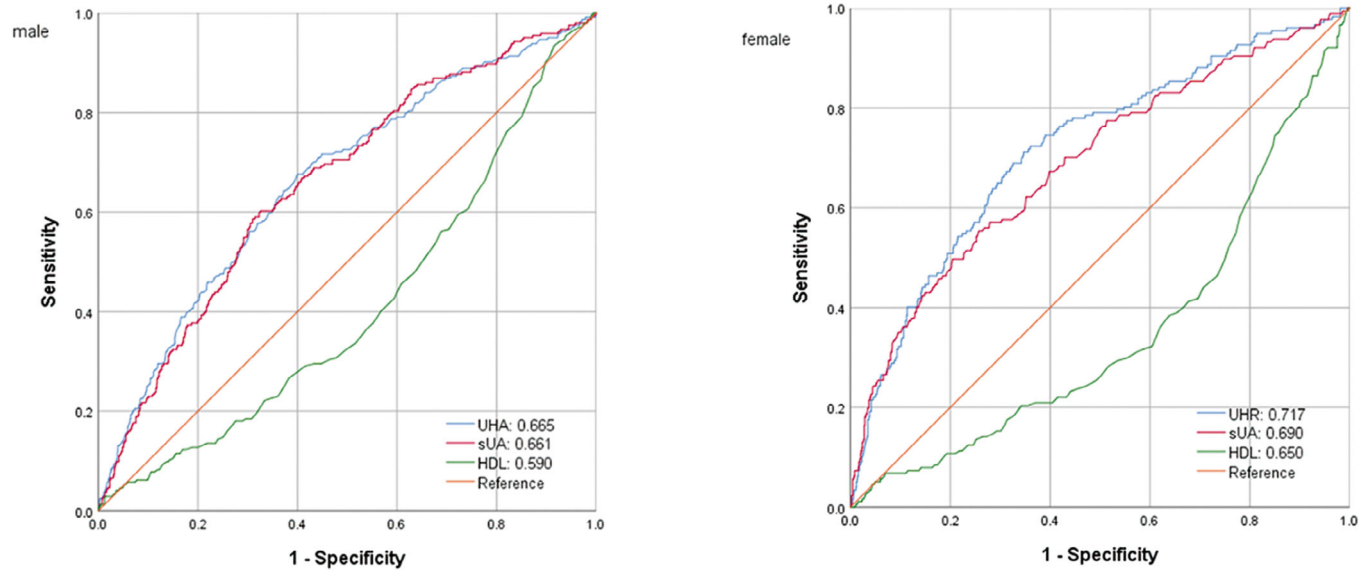

Figure 3 | ROC analysis of UHR, uric acid, and HDL-C to insulin resistance among patients with type 2 diabetes mellitus.

Table 4 | The results of ROC analysis of UHR for the diagnosis of insulin resistance

Nutritional indices	Cut-off	Sensitivity (%)	Specificity (%)	Youden's index	AUC	95% CI
Male	19.0	60.2	67.5	0.277	0.665	0.627–0.703
Female	13.6	71.2	65.3	0.365	0.717	0.674–0.760

resistance by 1.36-times. Another meta-analysis, Kodama *et al.*[23] revealed that serum uric acid levels increase the risk of type 2 diabetes mellitus by 17% for every 1 mg/dL increase. Additionally, an increase in HDL-C is considered to be a protective factor against insulin resistance[24]. Given that uric acid or HDL-C alone can serve as biomarkers for insulin resistance, we investigated whether the combination of these two indicators, known as UHR, could better identify insulin

resistance in patients with type 2 diabetes mellitus. As shown in Figure 3, our results showed that UHR had the largest AUC compared with uric acid and HDL-C alone, indicating its superior performance in detecting insulin resistance.

Previous studies have reported the usefulness of UHR in predicting metabolic syndrome. Kocak *et al.* found that serum UHR could effectively predict metabolic syndrome in individuals with diabetes mellitus in Turkey[14]. Similarly, Yazdi *et al.* discovered that UHR could be used to screen for and to diagnose metabolic syndrome risks in Iranians without diabetes mellitus[25]. Furthermore, Kocak *et al.* demonstrated that UHR outperformed other established criteria, including uric acid, as a marker for metabolic syndrome[15]. In addition, Kosekli *et al.* conducted a study within a single institution, revealing a connection between UHR and nonalcoholic liver disease[16]. Furthermore, a cross-sectional study conducted among lean Chinese individuals also identified a relationship between UHR and nonalcoholic liver disease[17]. Moreover, a recent epidemiological study demonstrated that UHR can contribute to an increased inflammatory burden[13]. However, this study is the first to investigate the association between UHR and elevated HOMA-IR or the risk of insulin resistance in patients with type 2 diabetes mellitus. This association may be attributed to the accumulation of metabolic or inflammatory changes.

In addition, it was found that UHR is associated with various metabolic-inflammatory diseases. Studies conducted by Aktas *et al.* suggested that elevated UHR is an independent risk factor for poor blood pressure control in individuals with hypertension[26]. Lee *et al.* found that high UHR values were positively associated with incident ischemic heart disease in Koreans without diabetes mellitus[27]. Aktas *et al.* proposed that UHR can be utilized in the evaluation of diabetes mellitus control in males with diabetes mellitus[15]. Aktas *et al.* reported that UHR has an independent predictive role in diabetic kidney injury, and it has a significant correlation with other markers of kidney function[28]. Zhang *et al.* found a significant correlation between UHR and baPWV existed in females but not in males[29]. Another study by Ozge demonstrated a significant positive correlation between UHR and thyroid stimulating hormone (TSH), as well as a negative correlation with free T4 (FT4)[13]. indicating that UHR can serve as a reliable and valuable marker for Hashimoto's thyroiditis. Our results were consistent with the above studies. It was observed that there was a significant correlation between UHR and various factors including BMI, WC, SBP, DBP, HbA1c, and FPG in patients with type 2 diabetes mellitus. These results highlight the potential value of UHR in future clinical applications and warrant further promotion.

Subgroup analysis on age, BMI, HbA1c, and a history of hypertension was further explored. The correlation between UHR and insulin resistance was more obvious in patients with type 2 diabetes mellitus and a BMI $\geq$ 24 kg/m^2, age < 60 years old, HbA1c < 7%, and non-hypertension. Importantly, for the above population, the insulin resistance is often neglected. Accordingly, UHR should be regarded as an important factor to identify insulin resistance, especially for the above population.

Uric acid and HDL-c are used very widely as indicators in clinical practice. UHR usage is simple and low cost, which has a strong correlation with insulin resistance and has some predictive power. This allows clinicians to find insulin resistance in a timely manner in clinical work to delay or even to prevent the development of diabetes mellitus. It will improve the type 2 diabetes mellitus patient's life and treatment and save economic costs.

There are potential mechanistic explanations for the association between UHR and insulin resistance. Elevated levels of uric acid can increase oxidative stress in adipocytes by upregulating monocyte chemotactic protein-1 and downregulating adiponectin[30]. This pro-oxidative effect may promote the accumulation of adipose tissue[31,32], thus resulting in insulin resistance[33]. Furthermore, uric acid-induced reduction in nitric oxide levels can impair glucose uptake by skeletal muscle, further exacerbating insulin resistance[31]. Studies have demonstrated that a reduction of uric acid levels through xanthine oxidase inhibitors and uricosuric agents can reverse insulin resistance in conditions such as fructose-induced metabolic syndrome and leptin receptor-mediated obesity[30,33–35]. HDL-C has the effects of reverse transport of cholesterol, which can reduce atherosclerosis, anti-thrombosis, anti-inflammation, vasodilation, and antiapoptosis[36]. Given that UHR is a fusion of the inflammatory response and lipid metabolism, the findings from our study suggest that UHR can potentially serve as a possible indicator for insulin resistance.

The advantage of this study is that the subjects were well characterized on the basis of a large population and different indicators were corrected in the model, thus improving the reliability of the results. However, this study also has some limitations. First of all, the causal relationship between UHR and insulin resistance cannot be determined through cross-sectional studies. Secondly, we recommend using HOMA-IR to evaluate insulin resistance. However, HOMA-IR has been associated with FPG, which is closely linked to liver IR, but not to muscle IR[37]. Further research is required to examine the relationship between UHR and insulin resistance by taking advantage of gold standard hyperinsulinemic-euglycemic clamp. Thirdly, the study population is limited to patients with type 2 diabetes mellitus. Therefore, a further prospective cohort study is necessary to confirm and promote the current findings in a larger population, including those without diabetes.

In conclusion, our large-scale cross-sectional study shows that UHR is a novel and practical biomarker for systemic inflammation, which is independently and positively correlated with insulin resistance, and appears to have higher insulin resistance AUC values than UA or HDL-C alone.

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DISCLOSURE

The authors declare that they have no conflict of interest.
Approval of the research protocol: This study has been approved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University.
Informed Consent: The written informed consent of all subjects was obtained following the Declaration of Helsinki.
Approval date of Registry and the Registration No. of the study /trial: LCKY2020-01.
Animal Studies: N/A.

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