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ORIGINAL RESEARCH

MHR Was Associated with Hyperuricemia Risk in Patients with Type 2 Diabetes Mellitus: The Mediating Effect of Body Mass Index

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Background: The monocyte-to-high-density lipoprotein cholesterol ratio (MHR) reflects systemic inflammation, combining the pro-inflammatory role of monocytes with the anti-atherogenic and anti-inflammatory properties of HDL-cholesterol. Prior studies have established MHR as an independent predictor of hyperuricemia (HUA) prevalence. Emerging evidence further identifies MHR as a potential biomarker for early type 2 diabetes mellitus (T2DM) screening, likely mediated through its association with insulin resistance. Therefore, our study specifically investigates the relationship between MHR and HUA in a T2DM population.

Methods: This cross-sectional study enrolled 1,261 T2DM patients. Logistic regression assessed associations between MHR and HUA. Mediation analysis evaluated body mass index (BMI) as a mediator. Restricted cubic spline (RCS) analysis examined nonlinear relationships. Receiver operating characteristic (ROC) curves compared predictive performance.

Results: Elevated MHR (adjusted OR = 2.040, 95% CI: 1.023 to 4.071, $p < 0.05$) was independently associated with HUA risk. BMI mediated 18.59% of the associations for MHR, respectively. RCS analysis revealed nonlinear patterns, with HUA risk increasing notably when MHR > 0.47. In ROC analysis, MHR demonstrated significant predictive ability for HUA, with an area under the curve (AUC) of 0.62.

Conclusion: Higher MHR was significantly associated with HUA risk in T2DM patients, with BMI serving as a key mediator. These markers may aid in early identification of patients at risk and underscore the importance of weight and inflammation control in HUA prevention.

Keywords: hyperuricemia, MHR, body mass index, mediation effect analysis, T2DM

Introduction

As we all know, an imbalance between the production and excretion of uric acid leads to HUA. HUA has become more common in China, rising from 11% to 14%.[1] The study of Sun et al found that the overall prevalence of HUA in diabetes was 21.2%.[2] HUA places a significant burden on people's lives and society. At the same time, several studies have suggested a link between HUA and a higher risk of heart disease, hypertension, obesity,[3,4] chronic kidney disease,[5] metabolic syndrome (MetS),[6] diabetes mellitus[7] and diabetic complications.[8–11]

Both monocytes and high-density lipoprotein are involved in the MHR, a newly discovered predictive measure for various diseases such as cardiovascular disease (CVD). Activated monocytes could produce a range of oxidizing and inflammatory molecules, which cause endothelial dysfunction, thrombus development, and the body's inflammatory response through interactions between the endothelium of the vessels and platelets.[12] High-density lipoprotein (HDL) particles play crucial roles in reverse cholesterol transport, inflammation modulation, and antioxidant defense.[13] HDL-associated proteins, including paraoxonase-1 (PON1) and myeloperoxidase (MPO), further influence oxidative stress and

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inflammation. Notably, PON1 exerts antioxidant effects, whereas MPO generates reactive species that impair HDL function.[14] HDL cholesterol (HDL-C) levels serve as a marker for cardiovascular disease (CVD) and chronic kidney disease (CKD) risk.[15,16] Impaired HDL function exacerbates lipid accumulation in renal and vascular tissues, suggesting that therapeutic strategies targeting HDL restoration may alleviate oxidative stress and inflammation.[16] Uric acid impairs β-cell function, reducing insulin secretion and β-cell mass. Hyperuricemia also triggers oxidative stress,[17] which is closely linked to insulin resistance and β-cell dysfunction. The resulting oxidative overload may further decrease insulin sensitivity, exacerbating metabolic disturbances in diabetes.[18] Elevated insulin levels due to insulin resistance and β-cell dysfunction can enhance renal uric acid reabsorption. This creates a vicious cycle, promoting mutual amplification between hyperinsulinemia and hyperuricemia through a feedback mechanism.[19]

Emerging evidence identifies the cumulative monocyte to high-density lipoprotein ratio (CumMHR) as a potential biomarker for early T2DM screening.[20] Prior studies have established MHR as an independent predictor of HUA prevalence.[21] Li et al found that MHR was significantly and positively correlated with serum uric acid levels in Chinese adults.[22] However, in the T2DM population, the relationship between MHR and HUA is still unclear. Therefore, our study specifically investigates the relationship between MHR and HUA in a T2DM population.

Methods

Study Population

This study is cross-sectional and single-center. The subjects are T2DM patients who were treated at our hospital's Department of Endocrine and Metabolism between 2021 and 2024. The following were the exclusion criteria: (1) age<18 years old or>80 years old, pregnancy; (2) incomplete information; (3) a history of severe hypoglycemia, type 1 diabetes (T1DM), other kinds of diabetes, or acute complications of diabetes tumor; (4) autoimmune diseases, acute and chronic diseases infected persons; (5) tumor diseases and blood system diseases; (6) severe liver function damage, severe renal function damage (including chronic kidney disease Phase 4–5); (7) other endocrine diseases, such as Primary hyperaldosteronism (PA), Cushing's Syndrome and pituitary disease; (8) Use drugs that affect uric acid levels, including diuretics, SGLT-2i (sodium-dependent glucose transporter 2 inhibitors), aspirin, and benzbromarone, febuxostat, Allopurinol. The current study included 1261 participants in total (Figure 1).

Covariates

With serum uric acid (SUA) values of 7.0mg/dL (420mmol/L), HUA was identified in both males and females[23]. T2DM was diagnosed using the 1999 World Health Organization criteria.[24] A self-reported history of hypertension, a diastolic blood pressure (DBP) of 90mmHg, and a systolic blood pressure (SBP) of 140mmHg were all considered indicators of hypertension.[25] A BMI of 28 kg/m^2 was considered obesity.[26] Total cholesterol (TC) ≧ 6.2, triglyceride (TG) ≧ 2.3, low-density lipoprotein cholesterol (LDL-C) ≧ 4.1, or the use of lipid-lowering medications were considered indicators of hyperlipidemia.[27] Every participant in this study underwent an ultrasound of their abdomen.

The following diagnostic standards were used to define kidney stones:[28,29] (1) the presence of a stone or stones with a diameter of at least 4 mm, as well as (2) the direct visualization of the stone or stones during the abdominal ultrasound test. Participants who responded "Yes" to the question, "Did your doctor ever tell you that you had gout?" were considered to have gout. Estimated glomerular filtration rate (eGFR) was calculated using the formula created by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[30]

On the morning following admission, all blood samples were taken from patients who had fasted overnight. Our hospital's biochemical center used standard methods to measure baseline monocyte, lymphocyte, neutrophil, and leukocyte counts, TC, TG, HDL-C, LDL-C, glycated hemoglobin A1c (HbA1c), alanine transaminase (ALT), aspartate aminotransferase (AST), creatinine (Cr), and SUA. Monocyte count (×10^9/L) / HDL-C (mmol/L) was used to calculate MHR.

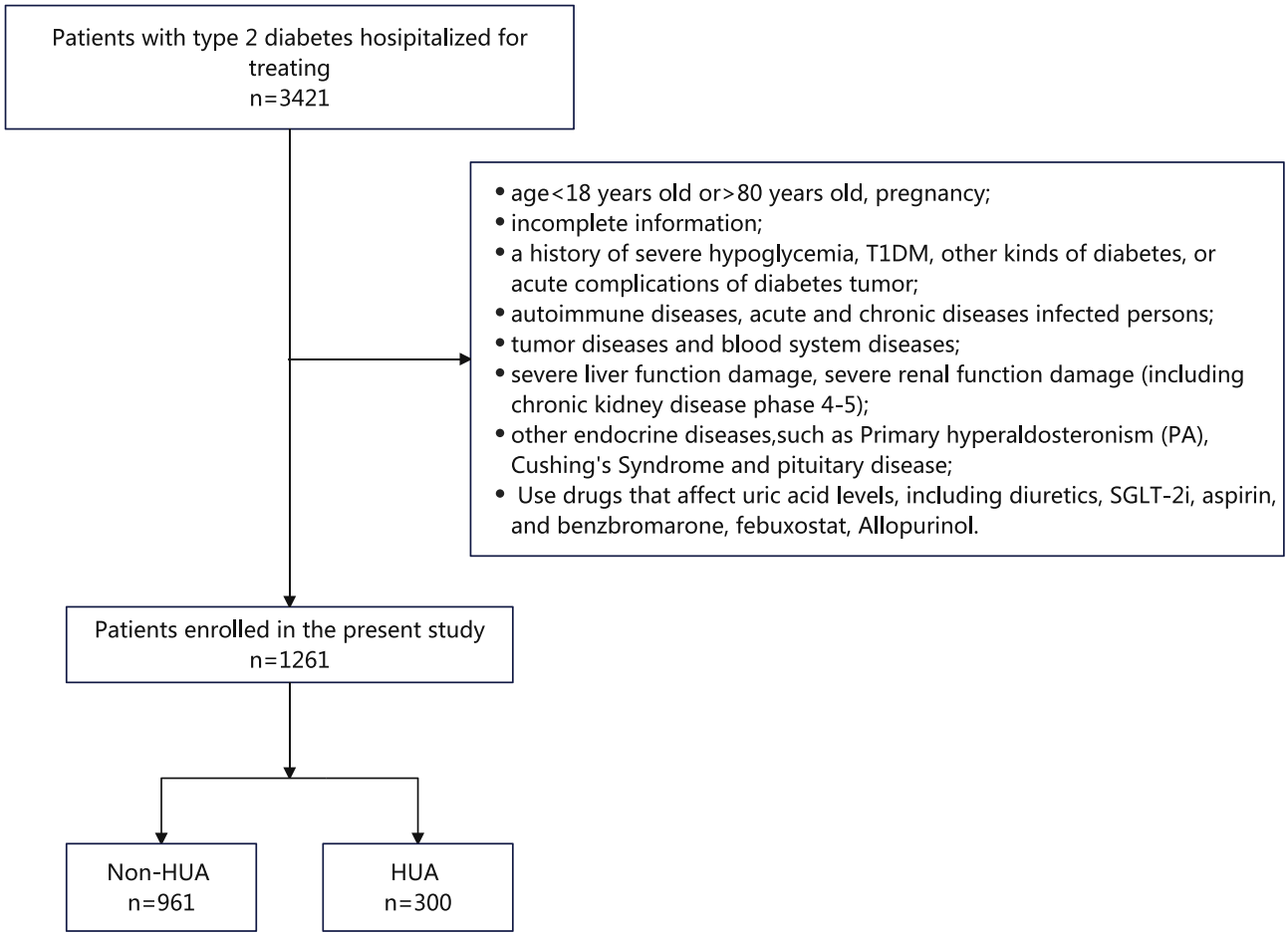

Figure 1 The study population flowchart.

Statistical Examination

Continuous variables are shown as median (with 25th and 75th percentiles), whereas categorical variables are shown as frequencies and percentages. For continuous variables, the Mann–Whitney U-test was employed, and for categorical variables, the χ^2 test. The relationship between MHR and HUA was evaluated using logistic regression analysis.

During the multivariate logistic regression analysis, factors such as age, duration, BMI, smoking, drinking, and family history of diabetes mellitus (DM), hypertension, hyperlipidemia, kidney stones, gout, eGFR, FBG, ALT, AST, GGT, and HbA1c were considered. To assess how well various characteristics could predict the existence of HUA, we performed an analysis of the area under the receiver operating characteristic (ROC) curve. To assess for variations among the various parameters on the ROC curves, we employed the non-parametric method of DeLong et al[31] (MedCalc). SPSS 27.0 was used for the statistical analysis, and $P < 0.05$ was the threshold for statistical significance. Using RCS analysis, the overall dose-response relationship between MHR and HUA risk was demonstrated. $P<0.05$ was established as the cutoff point for statistical significance.

Results

Baseline Characteristics of the Study Population

Table 1 displayed each patient's initial features. In the current study, 300 patients had HUA and 961 patients did not. Patients with HUA were younger and more likely to have gout, kidney stones, hypertension, and hyperlipidemia than those without HUA. Additionally, patients with HUA exhibited decreased eGFR and HDL-C but greater BMI, creatinine, ALT, AST, GGT, TC, and TG. Patients with HUA also had a higher family history of lipid-lowering medications and

Table 1 Characteristic of Subjects Stratified by HUA

Variables	Total (n=1261)	Normouricemia (n=961)	HUA (n=300)	*P* value
Male, n (%)	711 (56.4)	513 (53.4%)	198 (66%)	<0.001
Age (yr)	59 (48,68)	60 (50,68)	55 (40.25,66)	<0.01
Duration (yr)	8 (2,15.5)	9 (3,16)	6 (1,14)	<0.05
Height (cm)	169 (162,174)	168 (160,174)	170 (165,176)	<0.01
Weight (kg)	73 (64,83)	71 (62.75,80)	80 (70,90)	<0.01
BMI (kg/m^2)	25.66 (23.44,28.41)	25.25 (23.12,27.82)	27.26 (24.73,30.06)	<0.01
Smoking, n (%)	448 (35.5)	331 (34.4%)	117 (39%)	0.15
Drinking, n (%)	400 (31.7)	295 (30.7%)	105 (35%)	0.162
Family History of diabetes mellitus	409 (32.4)	296 (30.8%)	113 (37.7%)	<0.05
SBP (mmHg)	133 (123,145)	132 (122,145)	134 (124,146)	0.184
DBP (mmHg)	81 (74,89)	80 (74,88)	82 (76,90)	<0.05
Hypertension, n (%)	688 (54.6)	509 (53%)	179 (59.7%)	<0.05
Hyperlipidemia, n (%)	932 (73.9)	691 (71.9%)	241 (80.3%)	<0.05
Gout, n (%)	39 (3.1)	11 (1.1%)	28 (9.3%)	<0.001
Lipid-lowering drug (%)	932 (73.9)	691 (71.9%)	241 (80.3%)	<0.004
Scr (μmol/L)	60 (50,71)	58 (49,68)	68 (57,82)	<0.01
(eGFRml/min per 1.73 m^2)	103.95 (92.29,117.21)	104.61 (94.25,116.2)	101.41 (81.64,121.04)	<0.05
SUA (μmol/L)	324 (201,456)	324 (201,456)	324 (201,374)	0.267
FPG (mmol/L)	7.5 (5.9,9.6)	7.5 (6,9.6)	7.2 (5.8,9.48)	0.232
TC (mmol/L)	4.86 (4.15,5.555)	4.81 (4.09,5.52)	4.98 (4.23,5.77)	<0.05
TG (mmol/L)	1.76 (1.245,2.65)	1.62 (1.17,2.41)	2.24 (1.68,3.42)	<0.01
HDL-C (mmol/L)	1.02 (0.88,1.2)	1.05 (0.91,1.24)	0.95 (0.83,1.09)	<0.01
LDL-C (mmol/L)	2.97 (2.41,3.59)	2.97 (2.41,3.57)	2.99 (2.44,3.68)	0.359
ALT, U/L	21 (15,33)	20 (14,29)	24 (17,49.5)	<0.01
AST, U/L	18 (15,24)	17 (14,22)	20 (16,31)	<0.01
GGT, U/L	25 (17,39)	24 (17,35)	35 (22,60)	<0.01
HbA1c, (%)	8.3 (7,10.1)	8.4 (7.1,10.1)	8.1 (6.8,10)	0.127
WBC count (10^9/L)	6.19 (5.21,7.33)	6.12 (5.17,7.29)	6.44 (5.33,7.53)	<0.05
Monocyte count (10^9/L)	0.48 (0.4,0.58)	0.47 (0.39,0.57)	0.5 (0.42,0.61)	<0.05
Lymphocyte count (10^9/L)	1.94 (1.57,2.37)	1.93 (1.56,2.36)	1.96 (1.6,2.38)	0.435
Monocyte count (10^9/L)	3.4 (2.8,4.36)	3.44 (2.8,4.28)	3.56 (2.84,4.55)	0.127
MHR	0.47 (0.36,0.61)	0.45 (0.35,0.58)	0.52 (0.41,0.68)	<0.01

Notes: Data are presented as number (percentage) for categorical variables and as median (with 25th and 75th percentiles) for continuous variables. Comparisons for category variables between groups were tested by $\chi 2$ test and comparisons of continuous variables between groups were tested by Mann–Whitney test.

Abbreviations: HUA, hyperuricemia; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Scr, serum creatinine; SUA, serum uric acid; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AIT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-Glutamyl Transpeptidase; HbA1c, Hemoglobin A1c; WBC, white blood cell; MHR, Monocyte to high-density lipoprotein ratio; NHR, neutrophil to high-density lipoprotein ratio.

Table 2 Association Between MHR and the HUA in Participants with T2DM

Variables	Odds Ratio (95%)					
	Model 1	P value	Model 2	P value	Model 3	P value
MHR	4.314 (2.423 to 7.681)	<0.001	3.327 (1.789 to 6.186)	<0.001	2.04 (1.023 to 4.071)	0.043

Notes: Model 1: no adjustment; Model 2: adjusted for age, duration, BMI, smoking, drinking and family history of diabetes mellitus; Model 3: adjusted for all the factors in model 2 and hypertension, hyperlipidemia, kidney stones, gout, eGFR, FBG, ALT, AST, GGT, HbA1c.
Abbreviations: MHR, monocyte to high-density lipoprotein cholesterol ratio; HUA, hyperuricemia, T2DM, type 2 diabetes mellitus; BMI, body mass index; eGFR, estimated glomerular filtration rate;FBG, fasting blood glucose; AlT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-Glutamyl Transpeptidase; HbA1c, Hemoglobin A1c.

DM. Hematologically, patients with HUA had greater leukocyte, monocyte, lymphocyte, and neutrophil counts than those without. As a result, MHR was higher in HUA patients than in non-HUA patients.

Relationships Between MHR and the Incidence of HUA in T2DM Patients

To ascertain the relationships between MHR and HUA, we employed a logistic regression analysis. As shown in Table 2, the results showed that MHR was associated with HUA without adjusting. After adjusting age, duration, BMI, smoking, drinking and family history of DM, hypertension, hyperlipidemia, kidney stones, gout, eGFR, FBG, ALT, AST, GGT, HbA1c, OR was 2.040 (95% CI=1.023–4.071, p<0.05), which the presence of HUA was still associated with MHR. These results implied a relationship between MHR and the occurrence of HUA.

Figure 2 summarized the general characteristics of the study participants by age, gender, BMI, and HbA1c. Figure 2 showed that patients' MHR was lower (p<0.001) when their HbA1c was less than 7%. Compared to the males, the

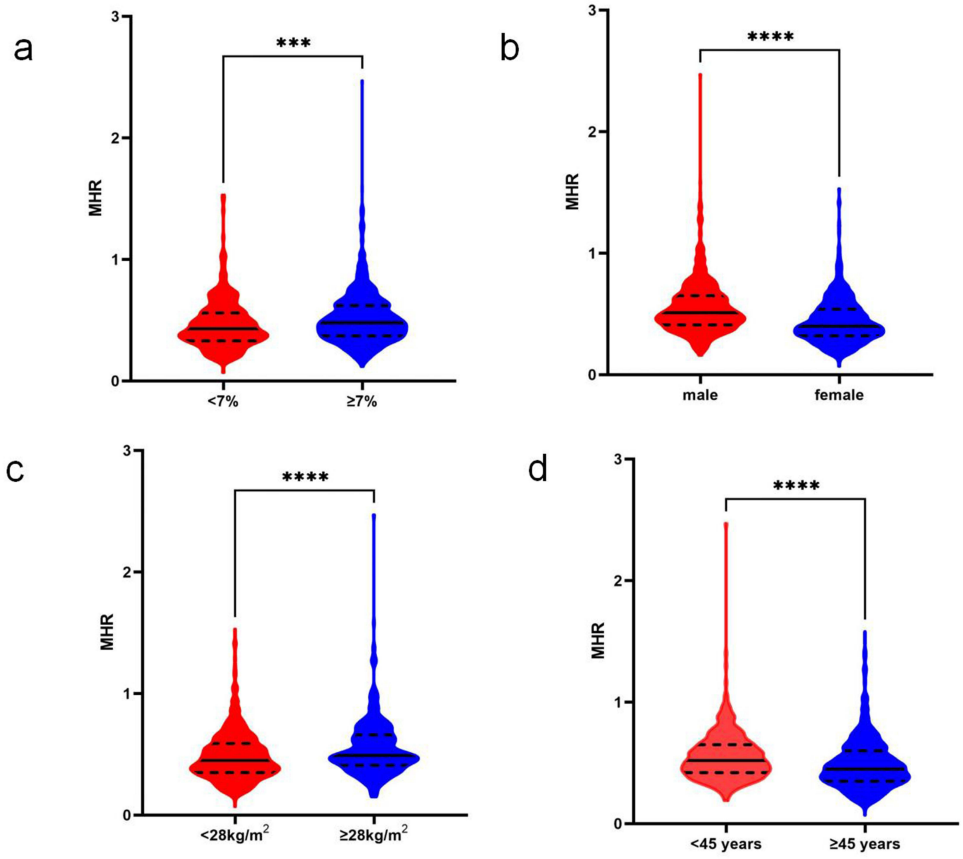

Figure 2 Comparisons of MHR levels according to HbA1c (**a**) gender (**b**) BMI (**c**) and age (**d**). (***p<0.001,****p<0.0001).

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females had a lower MHR. In addition, patients aged ≥ 45 had a lower MHR than those aged ≥ 45, and patients with a BMI < 28 had a lower MHR than those with a BMI ≥ 28 (p<0.001).

BMI's Mediating Role in the Relationships Between MHR and the Risk of HUA

Figure 3 showed an analysis of the mediating role of BMI in the relationship between MHR and the risk of HUA. Causal mediation analysis indicated that BMI partially mediated the association between MHR and HUA risk in patients with T2DM. The average causal mediation effect (ACME) was 0.29 (95% CI: 0.16–0.45), and the average direct effect (ADE) was 1.27 (95% CI: 0.67–1.87), with a total effect of 1.56. The proportion of the effect mediated by BMI was 18.59%, suggesting that BMI plays a modest but significant mediating role in the MHR-HUA pathway (all p < 0.001).

Nonlinear Effects of MHR on HUA: RCS Findings

Figure 4 revealed that the risk of HUA in patients with T2DM was strongly correlated with MHR. A nonlinear association between MHR and HUA risk was shown using restricted cubic spline analysis (p for overall = 0.005, p for nonlinear = 0.013). The risk of HUA increased at MHR>0.47, peaking at 0.73.

Predictive Performance of MHR for HUA in T2DM

Figure 5 revealed that MHR had significant discriminatory ability for HUA in patients with type 2 diabetes mellitus (T2DM). The area under the curve (AUC) for MHR was 0.62 (95% CI: 0.58–0.65), with a specificity of 71.9% and sensitivity of 46.3%, as was shown in Table 3. These results suggest that MHR demonstrated predictive performance in identifying HUA risk among T2DM patients.

Discussion

The association between MHR, BMI, and HUA risk was thoroughly examined in this cross-sectional study of 1261 adults from Tianjin University Medical General Hospital. To the best of our knowledge, this study may be the first to evaluate the mediating function of BMI in the associations between MHR and the risk of HUA. Given the dramatic increase in the incidence of HUA globally, our result highlights the importance of lowering MHR while losing weight in reducing the prevalence of HUA.

The inflammatory response and immunological state are intimately linked to the pathophysiology of HUA. Vascular smooth muscle cell (VSMC) proliferation is induced by soluble uric acid, according to studies.[32] Subsequent research showed that soluble uric acid, through the mitogen-activated protein kinase (MAPKs) pathway, mediates the increased proliferation of VSMC. Furthermore, uric acid causes vascular cells to become more inflammatory. Increased serum urate levels have been linked to inflammatory indicators.[33]

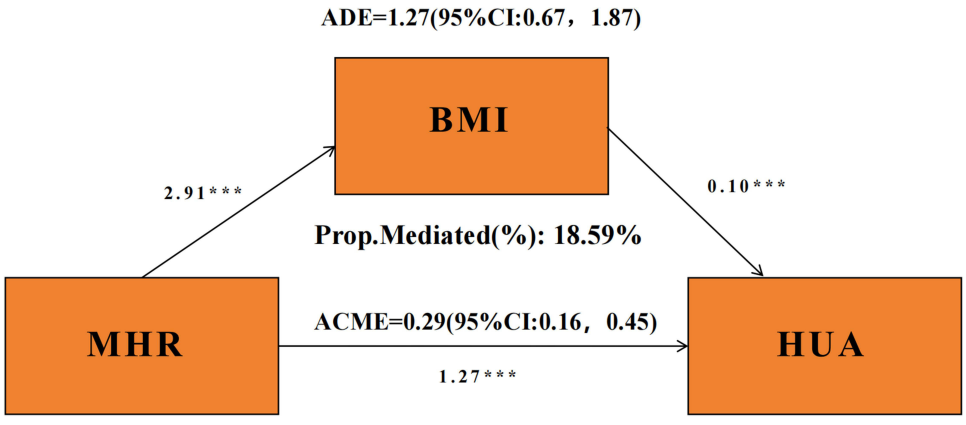

Figure 3 Mediation effect of BMI on the associations of MHR with HUA risk. Average Causal Mediation Effect (ACME) refers to the indirect effect; Average Direct Effect (ADE) refers to the direct effect, and the mediation percentage represents the proportion of the indirect effect to the total effect (sum of indirect and direct effects). ***P-value <0.001.

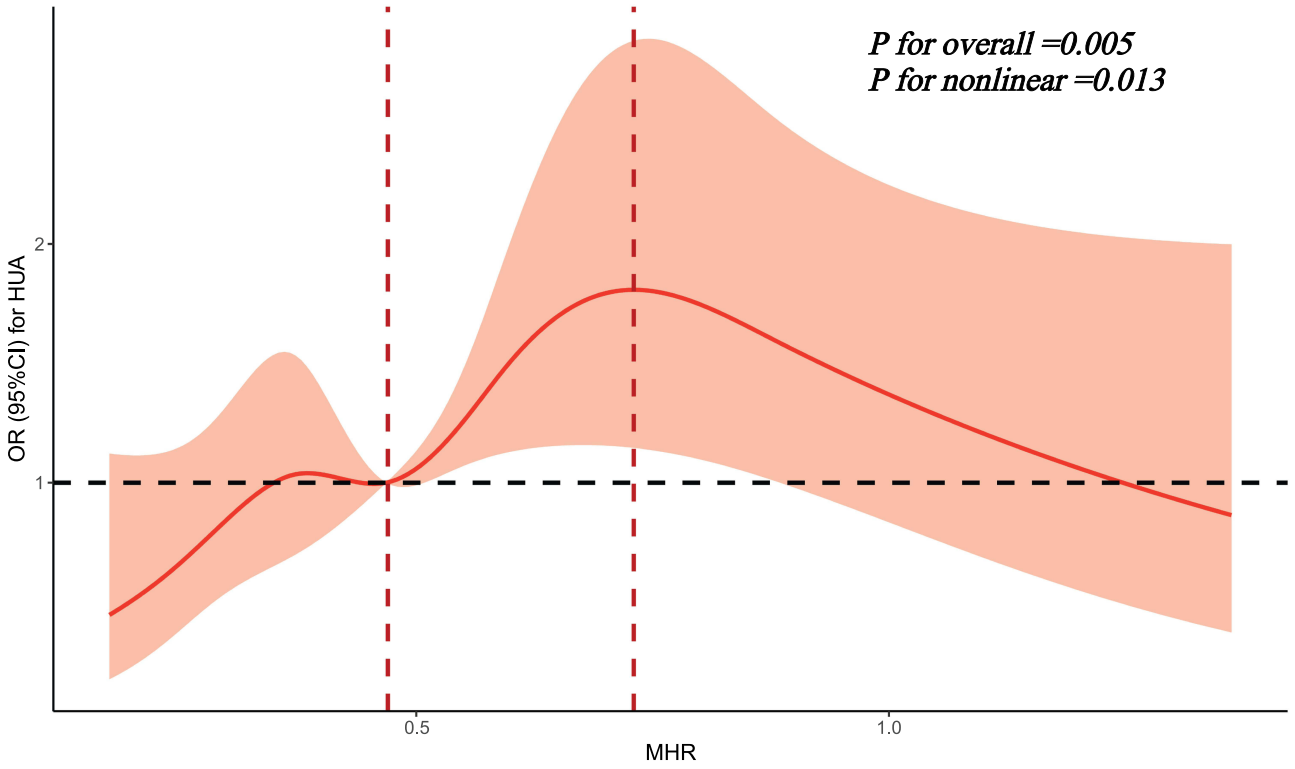

Figure 4 Associations of MHR with HUA in T2DM patients. Restricted cubic splines were used to assess the dose–response associations of MHR with HUA in T2DM patients after adjusted for age, duration, BMI, smoking, drinking and family history of diabetes mellitus, hyperlipidemia, kidney stones, gout, eGFR, FBG, ALT, AST, GGT, HbA1c.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; AlT, alanine transaminase; AST, aspartate aminotransferase; GGT, γ-Glutamyl Transpeptidase; HbA1c, Hemoglobin A1c.

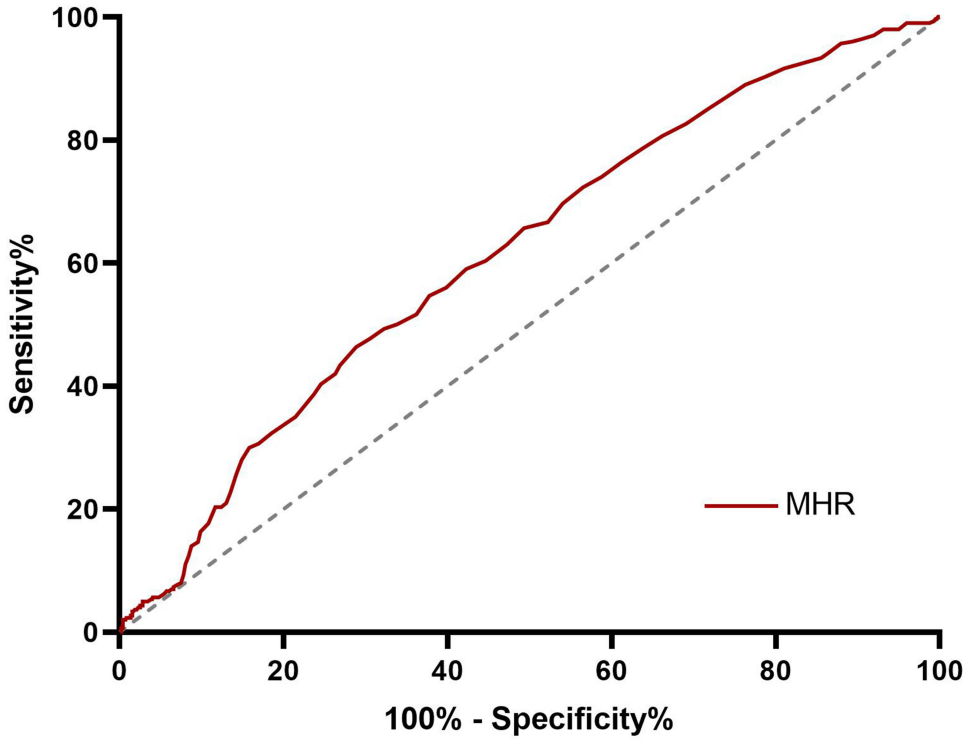

Figure 5 Receiver operating characteristic curve analysis of MHR in predicting hyperuricemia.

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Table 3 Receiver Operating Characteristic Curve Analysis of MHR and Its Predictive Value for HUA in Patients with T2DM

	AUC (95% CI)	P value	Sensitivity (%)	Specificity (%)
MHR	0.62 (0.58 to 0.65)	<0.0001	46.3	71.9

Abbreviations: MHR, monocyte to high-density lipoprotein cholesterol ratio; HUA, hyperuricemia; T2DM, type 2 diabetes mellitus; AUC, area under the curve.

SUA and monocytes mutually influence each other. According to recent research, soluble uric acid directly affects human primary peripheral blood mononuclear cells (PBMCs) to produce proinflammatory cytokines, and following ex vivo stimulation, PBMCs from HUA patients produce more of these cytokines than healthy controls.[34,35] Monocytes can elevate SUA levels by promoting the production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-1β, IL-12, and IL-23,[36] while reducing anti-inflammatory cytokine (IL-10) levels.[37] TNF-α not only directly damages vascular endothelial cells but also induces hyperinsulinemia. Elevated insulin and proinsulin stimulate renal tubular sodium-hydrogen exchange, increasing uric acid reabsorption and hydrogen excretion. The resulting rise in SUA further stimulates monocytes to release inflammatory cytokines, creating a positive feedback loop that perpetuates SUA elevation.[38]

Beyond its pro-inflammatory effects, SUA also exhibits immunosuppressive properties in monocytes.[39] An in vitro study by Qiu et al demonstrated that SUA inhibits Toll-like receptor (TLR) signaling in monocytes, thereby impairing classical monocyte migration.[40] High-density lipoprotein (HDL), an anti-inflammatory factor, suppresses monocyte activation, adhesion, and migration while inhibiting pro-inflammatory cytokine production.[41,42] Consequently, HDL-C serves as a protective factor against elevated SUA. Collectively, these findings indicate a positive correlation between the MHR and SUA levels.

MHR integrates several parameters and is quick and easy to calculate. It can more properly depict the inflammatory changes in HUA because it reflects the complementary interactions between many pathways, which is a benefit over using a single indication. According to our research, patients with T2DM who had MHR had a considerably higher chance of developing HUA. In particular, the risk of HUA increased with MHR > 0.47.

Furthermore, this study discovered that BMI is a significant mediating factor in the associations between MHR and the risk of HUA. Our results are supported by certain existing findings. On the one hand, uric acid levels and the risk of HUA are strongly correlated with BMI, a measure of obesity.[43–48] A study including 39,736 Chinese participants from Jiangsu Province found that uric acid concentrations were significantly greater in obese people than in underweight ones. Additionally, the study showed that uric acid levels rose linearly with BMI. Overweight people were about 2.98 times more likely to have HUA than underweight people, and obese people were about 5.96 times more likely to have HUA.[47] Our results suggested that managing weight would be a useful strategy to lower the risk of HUA and the negative health consequences brought on by elevated uric acid levels.

Some possible biological pathways should receive special attention, even though the precise mechanism underlying the mediating effect of BMI on the favorable associations of MHR with HUA risk is still unknown. First, a protracted state of inflammation may cause an inflammatory reaction in adipose tissue, resulting in adipocyte malfunction that impacts hormone secretion[49,50] and lipid metabolism,[51] thereby contributing to the development of obesity.[52] Secondly, by altering cell structure and function, oxidative stress may potentially contribute to tissue damage and metabolic problems.[53,54] Lastly, the level of inflammation may also disrupt the balance of gut microbiota, resulting in dysbiosis, which can affect uric acid metabolism and weight control by affecting energy metabolism and nutrient absorption.[55,56] These intricate biological processes interact with one another and raise the body mass index. Through some pathways, the elevated BMI may impact the metabolism of uric acid.[57]

There might be some advantages to our study. First of all, this is the first study to examine the relationship between MHR and the risk of HUA in T2DM. Secondly, this study was the first to evaluate the mediating role of BMI in the relationship between MHR with HUA risk. Our findings suggested that managing weight could be a useful strategy to lower the risk of HUA.

However, our study still had several limitations. Firstly, the cross-sectional study design makes it impossible to prove a causal link between the risk of HUA and MHR. Secondly, there is still a chance that unmeasured confounding variables could interfere with our results, even though we used a variety of covariates to account for potential confounders in our study. Thirdly, limitations include unmeasured diabetic complications (eg CKD), which may affect SUA levels and the observed relationships. Further research is needed to systematically investigate diabetic complications (eg CKD, neuropathy, retinopathy), which would help refine the relationship between MHR and HUA in patients with varying diabetes outcomes.

Lastly, while current evidence indicates that various antihypertensive agents differentially modulate serum uric acid (SUA) levels - with diuretics, β-blockers, and α-1 adrenergic antagonists potentially elevating SUA through reduced glomerular filtration rate, while calcium channel blockers, ACE inhibitors, and specific angiotensin receptor blockers (particularly losartan) appear neutral.[58] The retrospective nature of our investigation precluded a comprehensive analysis of antihypertensive medication regimens. This important pharmacologic confounder warrants systematic evaluation in future prospective studies to elucidate the potential mediating effects of antihypertensive therapies on uric acid metabolism. Future studies should evaluate these interactions.

Conclusion

When MHR is in the interval of 0.47 to 0.73, adults who were exposed to higher MHR had a higher chance of developing. The associations between MHR and the risk of HUA were significantly mediated by BMI, indicating that losing weight and lowering MHR may be useful strategies to lower the risk of HUA for T2DM patients. A future longitudinal study with a larger sample size is needed to explore this association further. Additionally, although BMI appears to mediate this relationship, further research is needed to elucidate the underlying biological mechanisms.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The 1964 Helsinki Declaration, its subsequent revisions, or similar ethical guidelines were adhered to in all study operations. The Tianjin Medical University General Hospital's institutional review board examined and approved studies involving human subjects (Approval number: IRB2024-YX-558-01). All participants gave their informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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