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Innovative Insights: The Role of Serum Uric Acid to High-Density Lipoprotein Cholesterol Ratio in Inflammatory Cardio-metabolic Disorders with a Bibliometric Analysis

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ABSTRACT

Introduction: Serum uric acid (UA) to high-density lipoprotein cholesterol (HDL-C) ratio (UHR) has recently been introduced as a novel indicator of inflammation. However, no reviews have summarized the applications of UHR. We conducted an overview to summarize and assess the current literature to evaluate UHR's clinical findings in cardio-metabolic and cardiovascular disorders.

Methods: The PubMed, Google Scholar, and Web of Science databases were searched for relevant articles pertaining to adults (age ≥18) up to December 2023. The search terms used were "uric acid" OR "serum uric acid" OR "serum UA" AND "high density lipoprotein" OR "high density lipoprotein cholesterol" OR "HDL" OR "HDL-C" OR "HDL-cholesterol. The final articles were imported to SCImago Graphica and VOSviewer visualization software for bibliometric analysis.

Results: A total of 27 eligible studies were included. The diseases in which UHR was evaluated include non-alcoholic fatty liver disease (NAFLD), diabetes mellitus (DM) and insulin resistance (IR), hypertension (HTN), and cardiovascular diseases (CVDs). We summarized the various attributes of UHR concerning these diseases, highlighting promising findings and limitations. The bibliometric analysis revealed that the disorder most frequently investigated was DM and IR (33.33%), followed by CVDs (29.62%) and NAFLD (22.22%). Most participants in the studies were from China. Asia and Europe produced the highest number of publications, with both China and Turkey contributing 11 publications each.

Conclusion: It appears that the UHR, as an underutilized marker, is associated with cardio-metabolic disorders and CVDs. However, further investigations are requisite to ascertain the UHR prognostic significance for these conditions.

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Introduction

Cardio-metabolic disorders are a group of prevalent and preventable chronic diseases such as diabetes mellitus (DM), hypertension (HTN), insulin resistance (IR), non-alcoholic fatty liver disease (NAFLD), and vascular diseases, which leads to cardiovascular diseases (CVDs) (1). They are among the leading causes of mortality worldwide, resulting in more than 4.8 million deaths among U.S. adults (2). Despite the progression in prevention, the cardio-metabolic disorders burden continues to rise for almost all countries (3). It has been reported that inflammation plays a significant role in the etiology and progress of cardio-metabolic disorders and CVDs (4, 5). So far, the relationship of well-established marker of systemic inflammation such as C-reactive protein (CRP), erythrocyte sedimentation rate, interleukin (IL) -6, IL-8, and cytokine with cardio-metabolic disorders has been widely investigated. However, they provide direct evidence of ongoing inflammation (6-8). In addition to these conventional markers, several new indicators and indices such as neutrophil-to-lymphocyte, CRP-to-lymphocyte ratio, and systemic immune-inflammatory index have recently been introduced to represent the

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inflammation in the body (9, 10). Another novel indicator is the combination of serum uric acid (UA) and high-density lipoprotein cholesterol (HDL-C).

UA is the end product of purine metabolism, which is produced by both the exogenous purines and their endogenous metabolism, mainly in the human liver (11). Elevated serum UA levels have been closely linked to various metabolic disorders, including gout, CVDs, dyslipidemia, DM, and HTN (12). Furthermore, direct correlations have been observed between UA levels and inflammatory biomarkers, including CRP and tumor necrosis factor-α (13, 14).

HDL-C, often called "good" cholesterol, is essential in the movement of excess cholesterols from peripheral tissues to the liver via scavenger receptors (15). HDL-C also has other biological properties, including anti-apoptotic, antithrombotic, anti-inflammatory, and antioxidant effects (16). Notably, depending on the presence or absence of inflammatory conditions in the body, HDL-C can function as either an anti-inflammatory or pro-inflammatory marker. Thus, both the quantity and the quality of HDL-C particles are critical in determining their overall impact on health (17).

The serum UA to HDL-C ratio (UHR) has recently emerged as a novel biomarker for the assessment of inflammatory processes and metabolism, garnering significant focus in recent investigations with an emphasis on pathophysiological mechanisms and the progression of diseases, especially the cardio-metabolic ones. Therefore, in this overview, we elucidate the history of UHR as an inflammatory indicator and its clinical significance across a diverse range of cardio-metabolic disorders and CVDs. To the best of our knowledge, at the time of writing this article, no existing review article on this particular topic have been identified in the literature. Additionally, we conducted a bibliometric analysis to better understand the distribution of research in this area.

Materials and Method

In the present overview, to evaluate the application value of the UHR, we employed a comprehensive and literature search strategy across multiple electronic databases, including PubMed, Google Scholar, and Web of Science. In order to maximize retrieval of pertinent studies, we used specific search terms: “uric acid” OR “serum uric acid” OR “serum UA” AND “high density lipoprotein” OR “high density lipoprotein cholesterol” OR “HDL” OR “HDL-C” OR “HDL-cholesterol”.

After the initial search, titles and abstracts were screened and duplicates were removed. The inclusion criteria were as follows: 1. studies must be original research articles with observational designs such as case-control, cross-sectional, retrospective, or prospective cohort studies. 2. studies must involve adult populations aged over 18 years. 3. Studies had to report data on the UHR in relation to inflammatory cardio-metabolic disorders. To ensure an inclusive and broad review, no language restrictions were applied for eligible studies. The search period encompassed all publications up to December 2023. Then, the authors retrieved the full texts of the studies and assessed them for final eligibility based on predefined criteria (Figure 1).

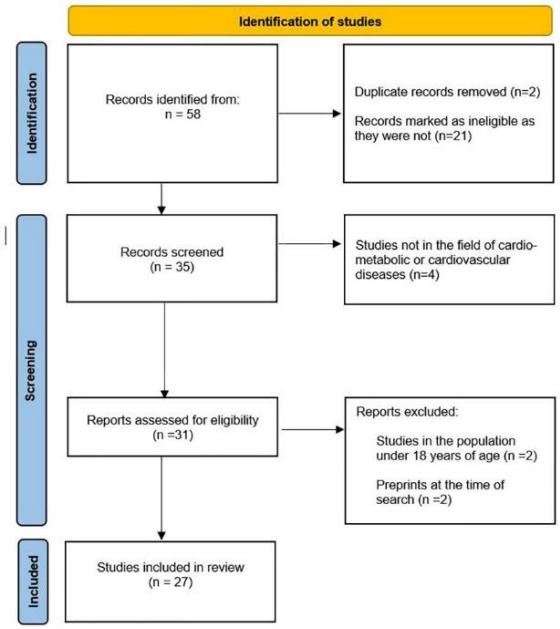

Figure 1. Diagram of the current study

For visualization and bibliometric analysis, the final studies were exported to bibliometric software tools such as SCImago Graphica (Beta 1.0.44) and VOSviewer (version 1.6.20). These tools facilitated the visualization of publication trends, collaboration networks, and keyword co-occurrences, providing insights into the UHR and its application in inflammatory cardio-metabolic disorders.

History of the UHR usage

The UHR, which is obtained as serum UA (mg/dl) divided by HDL-C (mg/dl), was proposed in 2019 by Kocak et al; 2019 (18). In an observational study involving subjects from the Turkish population with confirmed type 2 DM (T2DM), the UHR was determined to be markedly elevated in individuals

with poorly controlled T2DM compared to those with good glycemic control (14 ± 5.4% vs. 9.7 ± 3.7%, $P < 0.001$). A UHR exceeding 11% could 77% correctly identify the worse diabetic control (sensitivity of 77%), and 60% correctly identified subjects who were not in the category of worse diabetic control (specificity 60%) (area under the curve (AUC): 0.752, $P < 0.001$). Additionally, a UHR exceeding 10.6% could 83% correctly identify metabolic syndrome (MetS) and 71% correctly identified subjects without MetS, among patients with T2DM (AUC: 0.839, $P < 0.001$). However, it is notable that the study sample size was relatively small. Then, increased UHR levels have been discussed in other metabolic and inflammatory conditions such as DM (19), NAFLD (20), HTN (21), and cardiovascular events (22) (Figure 2).

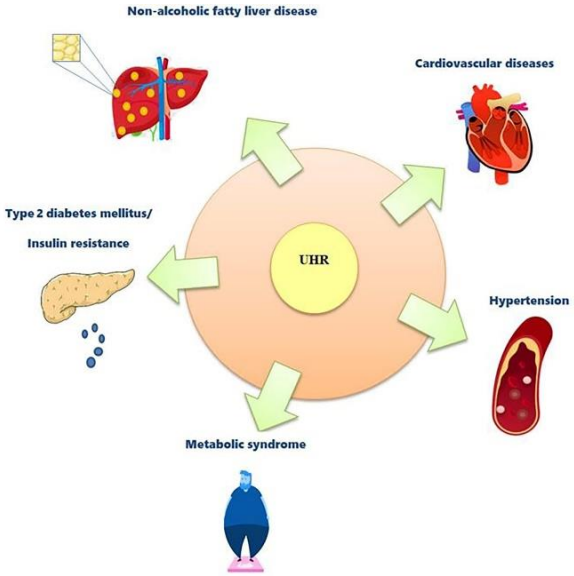

Figure2. UHR in cardio-metabolic and cardiovascular diseases

UHR and metabolic syndrome

Metabolic syndrome (MetS) contains cardio-metabolic risk factors that collectively elevate the risk for various health issues, including CVDs and T2DM (23). The components of MetS typically include impaired insulin sensitivity, high blood pressure, high triglycerides, low HDL-C, and central obesity (24). MetS is one of the most prevalent non-communicable disorders with increasing global prevalence and incidence (25). Research has consistently shown that MetS is a pro-thrombotic and pro-inflammatory condition, contributing to low-grade chronic inflammation and oxidative stress (26). Adipose tissue dysregulation, particularly in the context of abdominal obesity, has an important role in promoting inflammation associated with MetS (27). Clinical data indicate that circulating inflammatory biomarkers, such as CRP and high-sensitivity CRP, are linked to the inflammatory pathways involved in MetS (28). Since traditional inflammatory markers can be costly, it is essential to identify individuals at risk for MetS early. Using accessible markers to assess its inflammatory burden is crucial for preventing cardiovascular and cerebrovascular complications (29).

Yazdi et al; 2021, in an analysis of 817 non-diabetic individuals from southeastern Iran discovered that subjects with higher UHR were 2.9 times more likely to have MetS. Notably, this association was stronger than that of UA alone, but weaker than other components of MetS. They reported that subjects with a UHR exceeding 9.50%, could 71% discriminate between patients with MetS and subjects without MetS (AUC = 0.71) (30). Subsequently, Kolahi et al; 2023, conducted a study with a larger sample size (9,637 subjects) in northeastern Iran, confirming that a UHR above 9.5% displayed a sensitivity of 89.07% and specificity of 77.03% in discerning with MetS from those without. They also found that UHR increased with the severity of MetS ($P < 0.001$) (31). However, both studies utilized cross-sectional designs, limiting their ability to establish causality. Further longitudinal studies across different ethnicities are needed to clarify the association between UHR and MetS.

UHR and diabetes mellitus/ insulin resistance

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic condition that accounts for approximately 90% of all diabetics. The pathophysiology of T2DM is associated with insulin resistance (IR) and impaired insulin secretion (32). According to reports, by 2019, approximately 537 million individuals worldwide were affected by T2DM, which is a significant concern (33, 34). There is a strong connection between T2DM and chronic low-grade inflammation (34). Numerous studies have investigated the relationship between T2DM and inflammatory biomarkers. In a study by Aktas et al; 2020, involving a small sample size of 159 individuals, it was found that UHR levels were directly correlated with diabetes status, specifically fasting blood glucose (FBG) and glycosylated hemoglobin A1c (HbA1c) levels in diabetic males. They reported that a UHR exceeding 11.7% could 78% correctly predict poorly controlled T2DM 60% correctly predict

subjects who were not in the category of poorly controlled T2DM (AUC: 0.74, $P < 0.001$). They concluded that UHR could be utilized for diabetes control among T2DM men (19). One possible explanation for this finding is the association between diabetes and lower testosterone levels in men (35) which leads to enhanced systemic inflammation and cardiac disorders (36, 37).

Another study reported that in patients with T2DM, UHR exceeding 10.6% could 83% correctly predict subjects with MetS and 71% correctly predict subjects without MetS (AUC: 0.839, P <0.001) (18). A study by Kosekli et al; 2022, reported that there were positive correlations between UHR levels and cardio-metabolic factors such as HbA1c, FBG, waist circumference, and body mass index (BMI). Also, negative relationships were discovered between the UHR levels and glomerular filtration rate (GFR) (38). Another investigation showed that UHR was independently and positively associated with visceral fat area (VFA) among Chinese adults (18–70 yrs) who had T2DM (β= 0.230, $P < 0.001$) (39). A possible explanation is that VFA is correlated with increased serum UA and is also an independent predictor of hyperuricemia in diabetic subjects (40).

Studies in this area extend beyond the relationship between UHR levels and T2DM to include the impact of UHR on microvascular and macrovascular complications of diabetes. For instance, Uzeli et al; 2023, analyzed 150 subjects within the Turkish population and discovered that UHR were significantly higher in T2DM subjects with diabetic peripheral distal neuropathy (DPDN) compared to those with T2DM without DPDN and healthy controls ($P < 0.001$). However, no meaningful difference was detected between diabetic individuals without DPDN and healthy controls ($P = 0.457$). They also reported no association between UHR levels and diabetic neuropathy (OR = 0.881, 95% CI: 0.472–1.643, $P = 0.689$) (41). Due to the cross-sectional design, they could not discover causality between elevated UHR levels and DPDN.

A separate study from China involving 4,551 diabetic men and postmenopausal women reported direct associations between UHR levels and CVDs and chronic kidney disease (CKD), although UHR levels were not related to diabetic retinopathy (DR) (42). In contrast, Han et al; 2023, disclosed that UHR was significantly related to the risk of diabetic kidney disease (DKD) and kidney impairment. However, UHR had a lower AUC compared to serum UA in detecting kidney impairment (0.713 vs. 0.762), leading them to recommend routine measurement of UHR in individuals with DKD (43). Another Turkish study indicated that UHR is an independent predictor of diabetic kidney injury with the OR of 2.3 (44).

IR is pertaining to reduced insulin sensitivity, leading to an inability to decrease plasma glucose levels (45). IR arises from both genetic and environmental contributors and is associated with T2DM development, atherosclerosis, and HTN (46). The gold standard for assessing IR is the hyperinsulinemic-euglycemic clamp; however, it is not routinely utilized in clinical practice due to its labor-intensive nature, high cost, and accessibility issues (47). The homeostasis model assessment for insulin resistance (HOMA-IR) provides an alternative method for measuring IR, although it requires fasting plasma insulin levels, which are not typically measured in clinical settings (48). Therefore, a reliable, cost-effective, and easy-to-assess marker for diagnosing IR is highly desirable.

Recent research by Zhou et al; 2023, studied 2,545 individuals with T2DM and utilized the HOMA-IR method to assess IR. They found that UHR levels were significantly associated with IR in both genders after potential confounders adjustments (49).

UHR and non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is among the most common chronic liver disorders, characterized by the lipids accumulation in hepatic cells (50). A strong relationship has been reported between NAFLD and hepatocellular carcinoma (51). Additionally, NAFLD is related to the increased risks of extrahepatic disorders, such as T2DM, HTN, CVDs, CKD, and cancers (52, 53). Currently, liver biopsy is the gold standard method for NAFLD diagnosing. However, due to its invasive nature, complications, cost, and potential for sampling errors, it is not feasible to perform liver biopsies on every subject with suspected NAFLD (54), the early detection of NAFLD by a reliable marker is a high yield to control and manage the condition.

Recent reports suggest that UHR may be a promising marker for diagnosing and predicting NAFLD across different populations. A study involving 6,285 Chinese adults with a BMI <24 kg/m^2 found that UHR is an independent indicator for the NAFLD risks. This study also discovered that UHR was significantly associated with NAFLD in subjects with normal serum UA and HDL-C levels (55). However, these findings were only applied to lean adults.

Xie et al; 2023, reported similar results among the American population. Notably, they used vibration-controlled transient elastography (VCTE) instead of liver ultrasonography for diagnosing NAFLD,

allowing them to assess both hepatic steatosis and fibrosis severity. After adjusting for multiple demographic and biochemical factors, they found significant positive associations between UHR heightened risk for NAFLD and liver steatosis severity. When adjusted for only age, gender, and race, UHR remained significantly associated with fibrotic nonalcoholic steatohepatitis, fibrosis, and cirrhosis. Subgroup analysis revealed that UHR was related to the risk of NAFLD specifically in women. Additionally, they conducted a receiver operating characteristic (ROC) analysis, which indicated that while the accuracy of UHR for diagnosing NAFLD improved, it remained insufficient (AUC = 0.6910) (56).

A case-control study involving 636 individuals with NAFLD and 754 controls discovered that UHR was associated with the NAFLD risk among the Chinese population, after accounting for multiple variables (57). Cui et al; 2023, provided further evidence supporting the association between UHR and NAFLD in Chinese with established T2DM and a BMI <24 kg/m^2. They demonstrated that UHR had significant positive association with NAFLD, even after adjusting for multiple confounders. The AUC for UHR in detecting NAFLD was 0.697, with a sensitivity of 0.761 and specificity of 0.553, which was greater than that for serum UA and HDL-C alone (58). Another study from Turkey retrospectively analyzed 117 subjects and reported that a UHR exceeding 9.6% could 73% correctly determine subjects with NAFLD (sensitivity of 73%), but lower ability to correctly determine subjects without NAFLD (specificity of 51%). Furthermore, they found a significant correlation between UHR and metabolic risk factors for hepatic steatosis (20). Zhu et al; 2022 conducted a retrospective study of 9,837 non-obese participants with normal lipid profiles, evaluated through hepatic ultrasound for diagnosing NAFLD. The study concluded that after adjusting for multiple potential confounders, including age, gender, hepatic and renal functional markers, and metabolic markers, increased quintiles of UHR were associated with a higher risk of incident NAFLD, with the highest risk observed in quintile 5 (HR: 1.76, 95% CI: 1.12–2.75). The AUC for UHR in predicting NAFLD was also exceeding that for UA and HDL-C alone (0.690 for UHR, 0.666 for UA, and 0.636 for HDL-C) (59). Collectively, these findings suggest that the identification of NAFLD could be facilitated by utilizing the UHR as a promising indicator, particularly in non-obese populations. However, it remains unclear whether UHR can accurately diagnose the severity of NAFLD, warranting further investigation. Additionally, since most of the studies mentioned were conducted in China, the results may not be generalizable to other ethnicities.

UHR and hypertension

Hypertension (HTN) is the leading risk factor for CVDs and a major preventable cause of all-cause mortality worldwide. Over the past 25 years, the numbers of individuals with HTN and the estimated associated morbidity and mortality have increased substantially, highlighting its emergence as a significant public health concern (60). Thus, discovering it's the risk and efficacious markers to decrease the burden on the population seem crucial. The pathophysiology of HTN is complex and multifactorial (61). Oxidative damage and vascular dysfunction are closely linked to inflammation and contribute to the pathogenesis of HTN by initiating inflammatory responses (62). Elevated serum UA levels have been implicated in atherosclerosis due to endothelial injury, which is significantly associated with HTN (63). Increased serum UA, even in the normal range, can also activate the renin-angiotensin system which leads to an increased risk of HTN development (64). Additionally, dyslipidemia is common in hypertensive individuals (65, 66). HDL-C protects endothelial cells through its anti-inflammatory properties by preventing the expression of adhesion molecules on the endothelium (67).

While the relationship between various inflammatory markers and HTN has been explored, studies focusing on UHR levels and their correlation with blood pressure are limited. Aktas et al; 2022, analyzed 444 individuals with primary HTN and 91 non-hypertensive controls and discovered that the presence of HTN was independently associated with UHR with the OR of 4.1. UHR was also correlated with poorly controlled HTN with the OR of 7.3. This suggests that uncontrolled HTN may involve low-grade chronic inflammation, which is more pronounced than in well-controlled cases (21). However, they enrolled the sample population from only one Turkish center. Another study by Han et al; 2023, indicated that among women of reproductive age (20–44 yrs) in the USA, UHR demonstrated an independent positive correlation with the prevalence of hypertension; however, this research involved a sample size which was relatively small (68). While this evidence supports the association of UHR with HTN, it cannot be used for clinical prediction or diagnosis of the condition. Clearly, more studies are needed in this area.

UHR and cardiovascular diseases

Epidemiological studies have indicated that cardiovascular diseases (CVDs) represent the primary cause of global death, attributed to approximately 31% of overall death (69, 70). While multiple CVDs risk factors have been identified, such as age, male sex, HTN, tobacco use, and obesity, recent reports have indicated that some individuals without these traditional risk factors could develop CVDs (71). Moreover, despite the development of advanced techniques and preventive strategies, CVDs patients are still at risk of adverse cardiac events (72). Therefore, identifying individuals at early risk of CVDs using accessible and reliable indicators is of significant clinical importance. To date, many studies have investigated the potential of the UHR as a novel marker of inflammation in various forms of CVDs.

Wang et al; 2023, found a nonlinear relationship between UHR and brachial-ankle pulse wave velocity among the Japanese population, with significant associations noted exclusively in women aged 24-84 yrs (73). A case-control investigation from Turkey revealed that UHR was significantly elevated in individuals with coronary fistula compared to a control group (74); However, this study was limited due to the single-center design and relatively small sample size of 111. In another Turkish study, Engin et al; 2023, analyzed 496 individuals with a history of coronary artery bypass grafting (CABG) surgery at least one year earlier, who had stable angina pectoris. They demonstrated that UHR levels could indicate saphenous vein graft occlusion (75). A report from China that analyzed 690 subjects who were candidates for fractional flow reserve (FFR) measurements found that UHR could predict functionally significant lesions in individuals with single-vessel coronary disease and intermediate stenosis. However, this study did not assess patients with multi-vessel disease (76). Aydın et al; 2021 evaluated 124 individuals with chronic total occlusion who underwent coronary angiography and reported that UHR was significantly associated with poor chronic collateral circulation with the odds of 0.8 ($P < 0.001$) (22). Yet, the small sample size and the single-center nature of this study pose limitations, as does the lack of consideration for the effects of antihypertensive medication on UA levels. Cizmecioglu et al; 2022, reported that dialysis patients with high UHR had elevated non-dipper heart rates, nocturnal heart rates, and nocturnal diastolic blood pressure. However, no significant connections were discovered between the UHR and pulse wave velocity (77). It is notable that all of the aforementioned studies were cross-sectional in nature, limiting their ability to establish causality.

In contrast, a prospective cohort study with a 50-month follow-up involving 16,455 Korean individuals without T2DM demonstrated a positive correlation between UHR and incidents of ischemic cardiac disease (even angina pectoris or acute myocardial infarction). Subgroup analyses indicated that females in the highest tertile of UHR were at a greater risk to develop ischemic cardiac disease compared to males (78). Additionally, a retrospective analysis of 480 Chinese population with acute myocardial infarction found that UHR could be an independent predictor for major cardiac events and mortality (79). However, this study did not assess the impact of variability in HDL-C and serum UA levels over the prognostic period.

In summary, while there is growing evidence supporting the role of UHR as a potential marker for CVDs, additional investigations are required to solidify its clinical utilities. The characteristics and results of studies regarding UHR in cardio-metabolic and CVDs are shown in Table 1.

Table 1. Characteristics and results of studies regarding UHR in cardio-metabolic and cardiovascular diseases

Authors, year, and country of study	Study design and population	Outcomes evaluated and methods of evaluation	Adjusted variables	Main findings
Metabolic syndrome				
Yazdi et al, 2021, Iran (30)	Observational (cross-sectional) study 817 subjects (96 with MetS and 721 without MetS)	MetS according to ATP-III criteria	-	UHR levels associated with MetS (OR=1.84; 95%CI: 1.27– 2.66).

Kolahi Ahari et al., 2023, Iran (31)	Retrospective cross-sectional study 9637 subjects (3824 with MetS and 5813 without MetS)	MetS according to IDF criteria	-	UHR was significantly associated with MetS (OR=0.55; 95%CI: 0.38, 0.79). UHR levels significantly increased as MetS components increased.
Diabetes and insulin resistance				
Aktas et al., 2020, Turkey (19)	Retrospective cohort study 159 male subjects (42 well-controlled T2DM, 82 poorly controlled T2DM, 35 control)	Diabetes control evaluated by HbA1c levels	-	UHR above 11.7% had 78% sensitivity and 60% specificity in predicting poorly controlled T2DM (AUC: 0.74, *P* <0.001, 95% CI: 0.65–0.83). UHR significantly and positively correlated with FBG (r=0.46, *P* <0.001) and HbA1c (r=0.59, *P* <0.001).
Kocak et al., 2019, Turkey (18)	Retrospective study 100 subjects with T2DM	MetS according to 2009 harmonized criteria of IDF, AHA/NHLBI, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity	-	UHR exceed 10.6% has 83% sensitivity and 71% specificity in predicting MetS (AUC: 0.839, *P* <0.001).
Kosekli et al., 2022, Turkey (38)	Retrospective case-control study 238 subjects (136 with new onset T2DM and 102 controls)	FBG and HbA1c levels were noted from the database.	-	UHR was significantly and positively correlated with HbA1c (r=0.75, *P* <0.001), FPG (r=0.64, *P* <0.001), WC (r=0.35, *P* <0.001) and BMI (r=0.20, *P*=0.002). UHR was significantly and negatively correlated with GFR (r=-0.24, *P* <0.001).
Sun et al, 2022, china (39)	Retrospective study 209 subjects aged 18–70 yrs with T2DM	VFA evaluated by bioelectrical impedance technology	-	UHR was positively associated with VFA (β =0.230, *P* <0.001).
Uzeli et al., 2023, Turkey (41)	cross-sectional study 150 subjects (50 diabetics with DPDN, 50 diabetics without DPDN, 50 healthy)	DPDN evaluated by electroneuromyography	-	UHR was not associated with diabetic neuropathy (OR=0.881; 95% CI: 0.472–1.643, *P*=0.689).
Xuan et al., 2023, China (42)	Cross-sectional study 4551 men and postmenopausal women with T2DM	CVD is defined as previously diagnosed with stroke, CAD, or PAD CKD is defined as eGFR≤60 mL/min/1.73 m2 and/or UACR ≥30 mg/g). DR evaluated by Fundus examination	Age, sex, BMI, smoke status and drink status, TC, LDL, HbA1c, eGFR (only in CVD and DR group), SBP, DBP, anti-diabetes agents	UHR was positively associated the diabetic-related vascular complications (OR=1.28; 95%CI: 1.02–1.61, *P* <0.05) for CVD and (OR=1.78, 95%CI: 1.39–2.27, *P* <0.001) for CKD. There was no association between UHR and DR.
Han et al., 2023, China (43)	1326 subjects with T2DM	DKD according to eGFR <60 mL/min/1.73 m^2 and/or AER >30 mg/24 h over 3 months Kidney Impairment according to eGFR <60 mL/min/1.73 m2	Age, sex, BMI, SBP, DBP, BUN, TG, TC, LDL, RC, FBG, HbA1C, AER	UHR was positively associated with the risk of DKD (OR=1.057; 95% CI, 1.039–1.076, *P* <0.05) and kidney impairment (OR=1.077; 95% CI, 1.012–1.147, *P*=0.020). UHR had a lower AUC than uric acid in detecting kidney impairment (0.713 vs 0.762).
Aktas et al., 2023, Turkey (44)	Retrospective study 287 subjects with T2DM	DKI	Age, duration of diabetes mellitus, HDL, eGFR, serum creatinine	UHR has an independent predictive role in DKI (OR=2.3; 95%CI: 1.94–2.74).
Zhou et al., 2023, China (49)	Cross-sectional study 2545 subjects with T2DM	IR evaluated by HOMA-IR	Age, BMI, duration of diabetes, WC, SBP, DBP, HbA1c, serum creatinine, serum albumin, UHR, drinking, smoking.	UHR was significantly correlated with IR (OR=1.06; 95%CI: 1.03–1.08 in males and OR=1.11; 95%CI: 1.08–1.15 in females).
Non-alcoholic fatty liver disease				
Zhang et al., 2020, China (55)	Retrospective cross-sectional study 6285 Chinese adults with BMI < 24 kg/m2 (654 with NAFLD and 5631 controls)	NAFLD evaluated by liver ultrasound	Age, gender, BMI, WC, SBP, DBP, γ-GT, TG, TC, FBG	UHR was independently associated with an increased risk of NAFLD (OR=1.105; 95% CI: 1.076–1.134; *P* <0.001).
Xie et al., 2023, USA (56)	Cross-sectional study 3766 American subjects	CAP and LSM evaluated by VCTE	Age, gender, race, hypertension, BMI, dyslipidemia drug, T2DM, smoke, physical activity, ALT, AST, ALP, γ-GT, TC, TG, serum creatinine, albumin, TB, HbA1c	UHR was significantly and positively associated with an increased risk of NAFLD (OR=1.331, 95% CI: 1.100-1.611; p=0.003). UHR was significantly and positively connected to the severity of hepatic steatosis (β =6.070; 95% CI: 3.896, 8.244; *P* <0.001).

Hui et al., 2023, China (57)	Case-control 1390 subjects (636 with NAFLD and 754 controls)	NAFLD evaluated by liver ultrasound	Age, sex, BMI, current smoking, diabetes, HTN, TG, TC, LDL	UHR was positively associated with the risk of NAFLD (OR=3.888; 95% CI : 2.324–6.504; *P* <0.05)
Cui et al., 2023, China (58)	Retrospective study 343 subjects with T2DM and BMI<24 kg	NAFLD evaluated by liver ultrasound	Age, gender, BMI, SBP, DBP, FIN, ALT, AST, γ-GT, TC, TG, LDL, FBG, BUN, creatinine, HOMA-IR	UHR was significantly associated with NAFLD (OR=3.73; 95% CI: 1.53–9.09).
Kosekli et al., 2021, Turkey (20)	Retrospective case-control study 117 subjects (60 with NAFLD and 57 controls)	NAFLD	-	UHR was significantly and positively correlated with hepatic steatosis risk factors (FBG (r=0.23, *P* =0.01), ALT (r=0.20, *P* =0.03), TG (r=0.4, *P* <0.001), body weight (r=0.39, *P* <0.001), WC (r=0.4, *P* <0.001), hip circumference (r=0.22, *P* =0.02), and BMI (r=0.29, *P* =0.002)).
Zhu et al., 2022, China (59)	Retrospective cohort study with 5-year follow-up 9837 non-obese subjects without dyslipidemia	The incidence of NAFLD was evaluated by liver ultrasound.	Age, gender, ALP, ALT, AST, ALB, TP, TB, BUN, FBG, TC, TG, LDL, BMI, SBP	Increased UHR was positively correlated with increased risk of NAFLD onset (HR=1.76; 95% CI: 1.12–2.75; *P* <0.001).
		Hypertension		
Aktas et al., 2022, Turkey (21)	Observational (retrospective cross-sectional) study 444 patients with primary HTN and 91 healthy control	HTN according to JNC VIII criteria	Age, BMI, FBG, serum creatinine, and WC	UHR was an independent risk factor for the presence of HTN (OR=4.1; 95%CI: 1.25–13.4). UHR was an independent risk factor for poor blood pressure control (OR=7.3; 95% CI: 3.90–13.63).
Han et al., 2023, China (68)	Observational (case-control) study 5485 women aged 20–44 yrs	HTN according to the American Heart Association/American College of Cardiology 2017 guideline	Age, race, education, marital status, DM, BMI, smoking status, TG, and total cholesterol.	UHR was positively associated with hypertension (OR=1.77; 95%CI: 1.36, 2.31)
		Cardiovascular diseases		
Wang et al., 2023, Japan (73)	Cross-sectional study 912 subjects of Japan's medical health checkup program	baPWV evaluated by automatic waveform analyzer	Age, sex, BMI, SBP, DBP, ALT, AST, γ-GTP, fatty liver status	UHR was positively correlated with baPWV (β=4.03; 95% CI: 0.76–7.30)
Mansiroglu et al., 2019, Turkey (74)	Case-control study 111 subjects (46 with CAF and 65 controls with normal coronary arteries)	CAF evaluated by coronary angiography	-	UHR was a significant predictor of CAF (OR=1.302; 95% CI: 1.023-2.123; *P* =0.024).
Engin et al., 2023, Turkey (75)	496 subjects with CABG surgery at least one year prior who had stable angina pectoris	SVG disease evaluated by coronary angiography (using the Judkin method)	-	UHR was an independent predictor for SVG disease development (OR=1.290; 95% CI: 1.060-1.897, *P* =0.008).
Li et al., 2022, China (76)	Retrospective cross-sectional study 690 subjects with ICS who underwent FFR measurements	FFR evaluated by QUANTIEN platform	Male, DM, smoking, WBC, monocyte, LDL, TBA, BMI ≥24	UHR >310.8 was independently associated with an FFR ≤0.8 (OR=7.171; 95% CI 4.168–12.338, *P* <0.001)
Aydın et al., 2021, Turkey (22)	124 subjects who underwent coronary angiography with the diagnosis of stable or unstable angina pectoris and had chronic total occlusion	CCC was evaluated by coronary angiography and was graded according to the Rentrop grading system	Age, gender	UHR was associated with poor CCC (OR=0.8; 95 % CI: 0.787–0.906, P <0.001). There was a moderate negative correlation between UHR and coronary collateral index (r=– 0.452, *P* <0.001).
Cizmecioglu et al., 2022, Turkey (77)	Retrospective cross-sectional study 124 subjects with CKD and 127 controls	BP, HR, and PWV were evaluated by a brachial-based ABPM oscillometric device.	–	Dialysis patients with high UHR had higher non-dipper HR (*P* =0.015), nocturnal HR (p=0.011), and nocturnal DBP (*P* =0.040). There was not an exact stage-specific result for pulse wave velocity.
Park et al., 2022, Korea (78)	Prospective cohort study with 50-month follow-up 6455 non-diabetic Korean subjects	Incident of IHD angina pectoris/ acute MI) during follow-up	Age, sex, BMI, smoking status, alcohol intake, physical activity, mean arterial blood pressure, FBG, and Log CRP level	High UHR values were positively associated with incidents of IHD HR=1.57; 95% CI: 1.01–2.4; *P* for Trend=0.011).
Yang et al., 2023, China (79)	Retrospective cohort study with 41-month follow-up 480 subjects with	MACEs all-cause death	Age, sex, BMI, LVEF, current smoking, multi-vessel disease, DM, HTN, dyslipidemia, prior PCI, prior	UHR independently predicted MACEs (HR=1.02; 95% CI: 1.01–1.04; *P* <0.05) and mortality (HR=1.04; 95% CI: 1.01-1.07; *P* <0.05).

	AMI		MI, WBC, FPG, TG, TC, LDL, eGFR, STEMI, LM/multi-vessel, proximal LAD, PCI/CABG, antiplatelet drugs, statins, beta-blockers, ACEI/ARB, uric acid-lowering drugs, and hypoglycemic drugs.	

Authors, year, and country of study	**Study design and population**	**Outcomes evaluated and methods of evaluation**	**Adjusted variables**	**Main findings**
Metabolic syndrome				
Yazdi et al, 2021, Iran (30)	Observational (cross-sectional) study 817 subjects (96 with MetS and 721 without MetS)	MetS according to ATP-III criteria	-	UHR levels associated with MetS (OR=1.84; 95%CI: 1.27– 2.66).
Kolahi Ahari et al., 2023, Iran (31)	Retrospective cross-sectional study 9637 subjects (3824 with MetS and 5813 without MetS)	MetS according to IDF criteria	-	UHR was significantly associated with MetS (OR=0.55; 95%CI: 0.38, 0.79). UHR levels significantly increased as MetS components increased.
Diabetes and insulin resistance				
Aktas et al., 2020, Turkey (19)	Retrospective cohort study 159 male subjects (42 well-controlled T2DM, 82 poorly controlled T2DM, 35 control)	Diabetes control evaluated by HbA1c levels	-	UHR above 11.7% had 78% sensitivity and 60% specificity in predicting poorly controlled T2DM (AUC: 0.74, *P* <0.001, 95% CI: 0.65–0.83). UHR significantly and positively correlated with FBG (r=0.46, *P* <0.001) and HbA1c (r=0.59, *P* <0.001).
Kocak et al., 2019, Turkey (18)	Retrospective study 100 subjects with T2DM	MetS according to 2009 harmonized criteria of IDF, AHA/NHLBI, the World Heart Federation, the International Atherosclerosis Society, and the International Association for the Study of Obesity	-	UHR exceed 10.6% has 83% sensitivity and 71% specificity in predicting MetS (AUC: 0.839, *P* <0.001).
Kosekli et al., 2022, Turkey (38)	Retrospective case-control study 238 subjects (136 with new onset	FBG and HbA1c levels were noted from the database.	-	UHR was significantly and positively correlated with HbA1c (r=0.75, *P* <0.001), FPG (r=0.64, *P* <0.001), WC (r=0.35, *P* <0.001) and BMI (r=0.20, *P*=0.002).

	T2DM and 102 controls)			UHR was significantly and negatively correlated with GFR (r=-0.24, *P* <0.001).
Sun et al, 2022, china (39)	Retrospective study 209 subjects aged 18–70 yrs with T2DM	VFA evaluated by bioelectrical impedance technology	-	UHR was positively associated with VFA (β =0.230, P <0.001).
Uzeli et al., 2023, Turkey (41)	cross-sectional study 150 subjects (50 diabetics with DPDN, 50 diabetics without DPDN, 50 healthy)	DPDN evaluated by electroneuromyography	-	UHR was not associated with diabetic neuropathy (OR=0.881; 95% CI: 0.472–1.643, *P*=0.689).
Xuan et al., 2023, China (42)	Cross-sectional study 4551 men and postmenopausal women with T2DM	CVD is defined as previously diagnosed with stroke, CAD, or PAD CKD is defined as eGFR≤60 mL/min/1.73 m2 and/or UACR ≥30 mg/g). DR evaluated by Fundus examination	Age, sex, BMI, smoke status and drink status, TC, LDL, HbA1c, eGFR (only in CVD and DR group), SBP, DBP, anti-diabetes agents	UHR was positively associated the diabetic-related vascular complications (OR=1.28; 95%CI: 1.02–1.61, *P* <0.05) for CVD and (OR=1.78, 95%CI: 1.39–2.27, *P* <0.001) for CKD. There was no association between UHR and DR.
Han et al., 2023, China (43)	1326 subjects with T2DM	DKD according to eGFR <60 mL/min/1.73 m^2 and/or AER >30 mg/24 h over 3 months Kidney Impairment according to eGFR <60 mL/min/1.73 m^2	Age, sex, BMI, SBP, DBP, BUN, TG, TC, LDL, RC, FBG, HbA1C, AER	UHR was positively associated with the risk of DKD (OR=1.057; 95% CI, 1.039–1.076, *P* <0.05) and kidney impairment (OR=1.077; 95% CI, 1.012–1.147, *P*=0.020). UHR had a lower AUC than uric acid in detecting kidney impairment (0.713 vs 0.762).
Aktas et al., 2023, Turkey (44)	Retrospective study 287 subjects with T2DM	DKI	Age, duration of diabetes mellitus, HDL, eGFR, serum creatinine	UHR has an independent predictive role in DKI (OR=2.3; 95%CI: 1.94–2.74).
Zhou et al., 2023, China (49)	Cross-sectional study 2545 subjects with T2DM	IR evaluated by HOMA-IR	Age, BMI, duration of diabetes, WC, SBP, DBP, HbA1c, serum creatinine, serum albumin, UHR, drinking, smoking.	UHR was significantly correlated with IR (OR=1.06; 95%CI: 1.03–1.08 in males and OR=1.11; 95%CI: 1.08–1.15 in females).

Non-alcoholic fatty liver disease				
Zhang et al., 2020, China (55)	Retrospective cross-sectional study 6285 Chinese adults with BMI < 24 kg/m2 (654 with NAFLD and 5631 controls)	NAFLD evaluated by liver ultrasound	Age, gender, BMI, WC, SBP, DBP, γ-GT, TG, TC, FBG	UHR was independently associated with an increased risk of NAFLD (OR=1.105; 95% CI: 1.076–1.134; *P* <0.001).
Xie et al., 2023, USA (56)	Cross-sectional study 3766 American subjects	CAP and LSM evaluated by VCTE	Age, gender, race, hypertension, BMI, dyslipidemia drug, T2DM, smoke, physical activity, ALT, AST, ALP, γ-GT, TC, TG, serum creatinine, albumin, TB, HbA1c	UHR was significantly and positively associated with an increased risk of NAFLD (OR=1.331, 95% CI: 1.100-1.611; p=0.003). UHR was significantly and positively connected to the severity of hepatic steatosis (β =6.070; 95% CI: 3.896, 8.244; *P* <0.001).
Hui et al., 2023, China (57)	Case-control 1390 subjects (636 with NAFLD and 754 controls)	NAFLD evaluated by liver ultrasound	Age, sex, BMI, current smoking, diabetes, HTN, TG, TC, LDL	UHR was positively associated with the risk of NAFLD (OR=3.888; 95% CI : 2.324–6.504; *P* <0.05)
Cui et al., 2023, China (58)	Retrospective study 343 subjects with T2DM and BMI<24 kg	NAFLD evaluated by liver ultrasound	Age, gender, BMI, SBP, DBP, FIN, ALT, AST, γ-GT, TC, TG, LDL, FBG, BUN, creatinine, HOMA-IR	UHR was significantly associated with NAFLD (OR=3.73; 95% CI: 1.53–9.09).
Kosekli et al., 2021, Turkey (20)	Retrospective case-control study 117 subjects (60 with NAFLD and 57 controls)	NAFLD	-	UHR was significantly and positively correlated with hepatic steatosis risk factors (FBG (r=0.23, *P* =0.01), ALT (r=0.20, *P* =0.03), TG (r=0.4, *P* <0.001), body weight (r=0.39, *P* <0.001), WC (r=0.4, *P* <0.001), hip circumference (r=0.22, *P* =0.02), and BMI (r=0.29, *P* =0.002)).
Zhu et al., 2022, China (59)	Retrospective cohort study with 5-year follow-up 9837 non-obese subjects without dyslipidemia	The incidence of NAFLD was evaluated by liver ultrasound.	Age, gender, ALP, ALT, AST, ALB, TP, TB, BUN, FBG, TC, TG, LDL, BMI, SBP	Increased UHR was positively correlated with increased risk of NAFLD onset (HR=1.76; 95% CI: 1.12–2.75; *P* <0.001).
		Hypertension		
Aktas et al., 2022, Turkey (21)	Observational (retrospective cross-sectional) study 444 patients	HTN according to JNC VIII criteria	Age, BMI, FBG, serum creatinine, and WC	UHR was an independent risk factor for the presence of HTN (OR=4.1; 95%CI: 1.25–13.4). UHR was an independent risk factor for poor

	with primary HTN and 91 healthy control			blood pressure control (OR=7.3; 95% CI: 3.90–13.63).
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Abbreviations: UHR: serum uric acid to high-density lipoprotein-cholesterol ratio; MetS: metabolic syndrome; IDF: international diabetes federation; OR: odds ratio; CI: confident interval; ATP-III: adult treatment panel; T2DM: type 2 diabetes mellitus; HbA1c: glycosylated hemoglobin A1c; AUC: area under the curve; FBG: fasting blood glucose; DKI: diabetic kidney injury; HDL: high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; CVD: cardiovascular disease; CAD: coronary arterial disease; PAD: peripheral artery disease; CKD: chronic kidney disease; DR: diabetic retinopathy; BMI: body mass index; TC: total cholesterol; LDL: low-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; IR: insulin resistance; HOMA-IR: homeostatic model assessment for insulin resistance; WC: waist circumference; VFA: visceral fat area; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement; DPDN: diabetic peripheral distal neuropathy; DKD: diabetic kidney disease; AER: albumin excretion rate; BUN: blood urea nitrogen; TG: triglyceride; RC: remnant cholesterol; NAFLD: non-alcoholic fatty liver disease; γ-GT: gamma-glutamyl transferase; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALB: albumin; TP: total protein; TB: total bilirubin; HR: hazard ratio; CAP: controlled attenuation parameter; LSM: liver stiffness measurement; VCTE: vibration controlled transient elastography; FIN: serum fasting insulin; JNC: joint national committee; HTN: hypertension; ICS: intermediate coronary stenosis; FFR: fractional flow reserve; WBC: white blood cell; TBA: total bile acid; HR: heart rate; PWV: pulse wave velocity; ABPM: ambulatory blood pressure monitoring; MACE: major adverse cardiovascular events; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; MI: myocardial infarction; STEMI: ST-segment elevation myocardial infarction; LM: left main coronary artery; LAD: left anterior descending artery; CABG: coronary artery bypass graft surgery; ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; IHD: ischemic heart disease; CRP: C-reactive protein; baPWV: brachial–ankle pulse wave velocity; CAF: coronary artery fistula; SVG: saphenous vein graft; CCC: chronic collateral circulation;

Results of the bibliometric analysis

Figure 3 illustrates the distribution of various cardio-metabolic and cardiovascular diseases investigated in the extracted articles. The disorder most frequently studied were DM and IR, accounting for 33.33% of the investigations, followed by CVDs at 29.62% and NAFLD at 22.22%. Figure 4 indicates an upward trend in the annual number of publications related to the UHR and its association with cardio-metabolic and CVDs from 2020 to 2023, reflecting growing interest in this research area. From the world map illustrating country contributions (Figure 5-A), it is evident that the majority of participants in these studies are from East Asia, with a significant representation from China. In terms of research output, both Asia and Europe have led in the number of publications, with China and Turkey each contributing 11 publications (Figure 5-B).

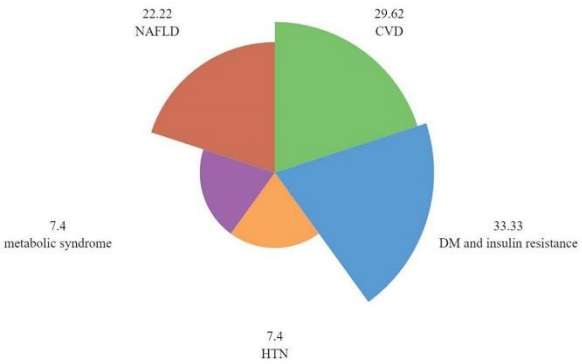

Figure 3. Distribution (%) of the cardio-metabolic and cardiovascular diseases from the extracted articles. Abbreviations: NAFLD: non-alcoholic fatty liver disease; CVD: cardiovascular diseases; DM: diabetes mellitus; HTN: hypertension.

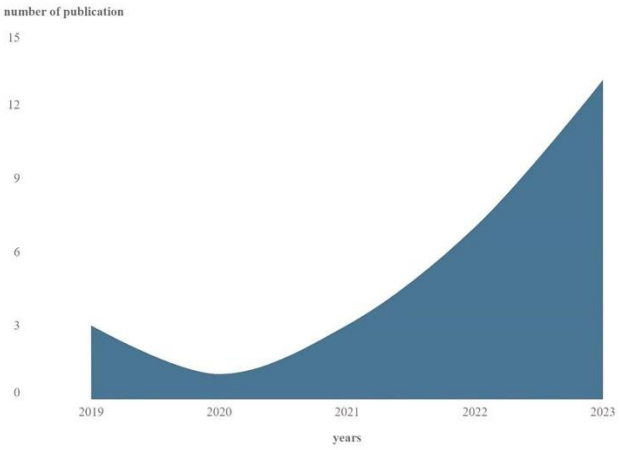

Figure 4. Trends in annual publications (per year) about UHR on cardio-metabolic and cardiovascular diseases from the UHR introduction until December 2023. Abbreviation: UHR: serum uric acid to high-density lipoprotein cholesterol ratio.

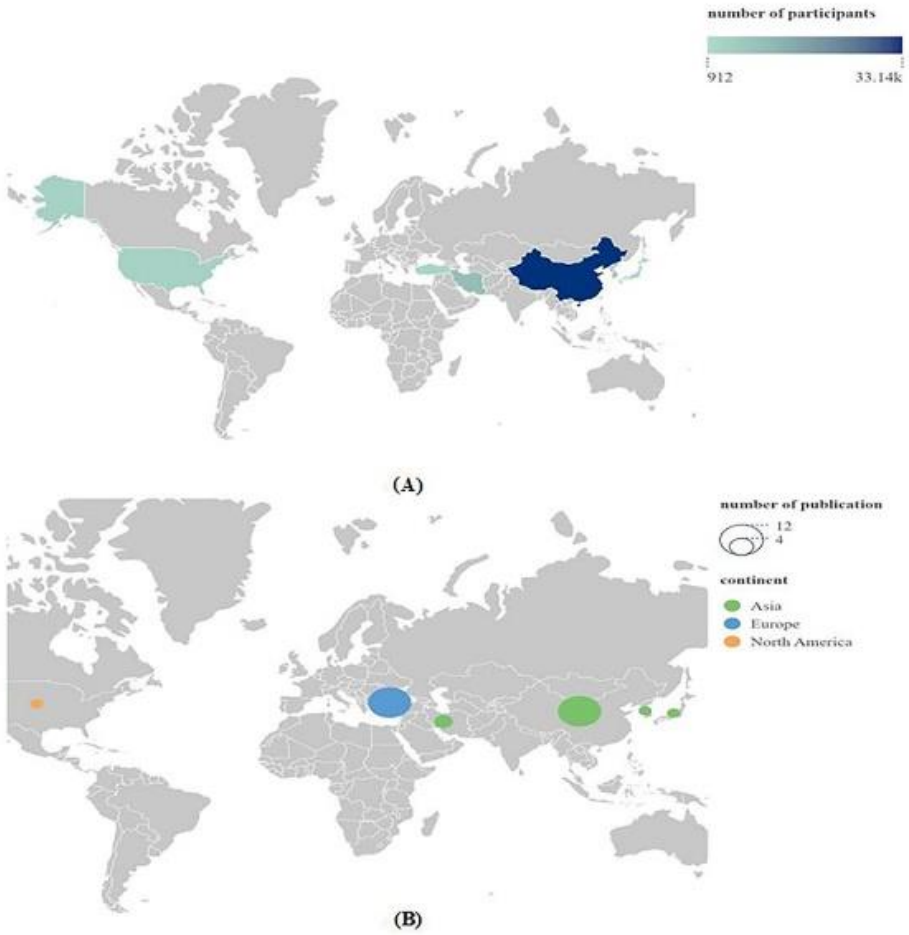

Figure 5. World map showing the number of cumulative participants in article creation by country, with darker shades indicating higher contributions (A) and contribution of each country, with circle sizes indicating the volume of publications. Different colors represent continents, highlighting regional research contributions (B).

Additionally, Figure 6 provides a co-occurrence view of the keywords used in these studies, highlighting the interconnectedness of various research themes within the framework of UHR and related diseases. This visualization can aid in identifying prevailing research trends and areas that may require further exploration.

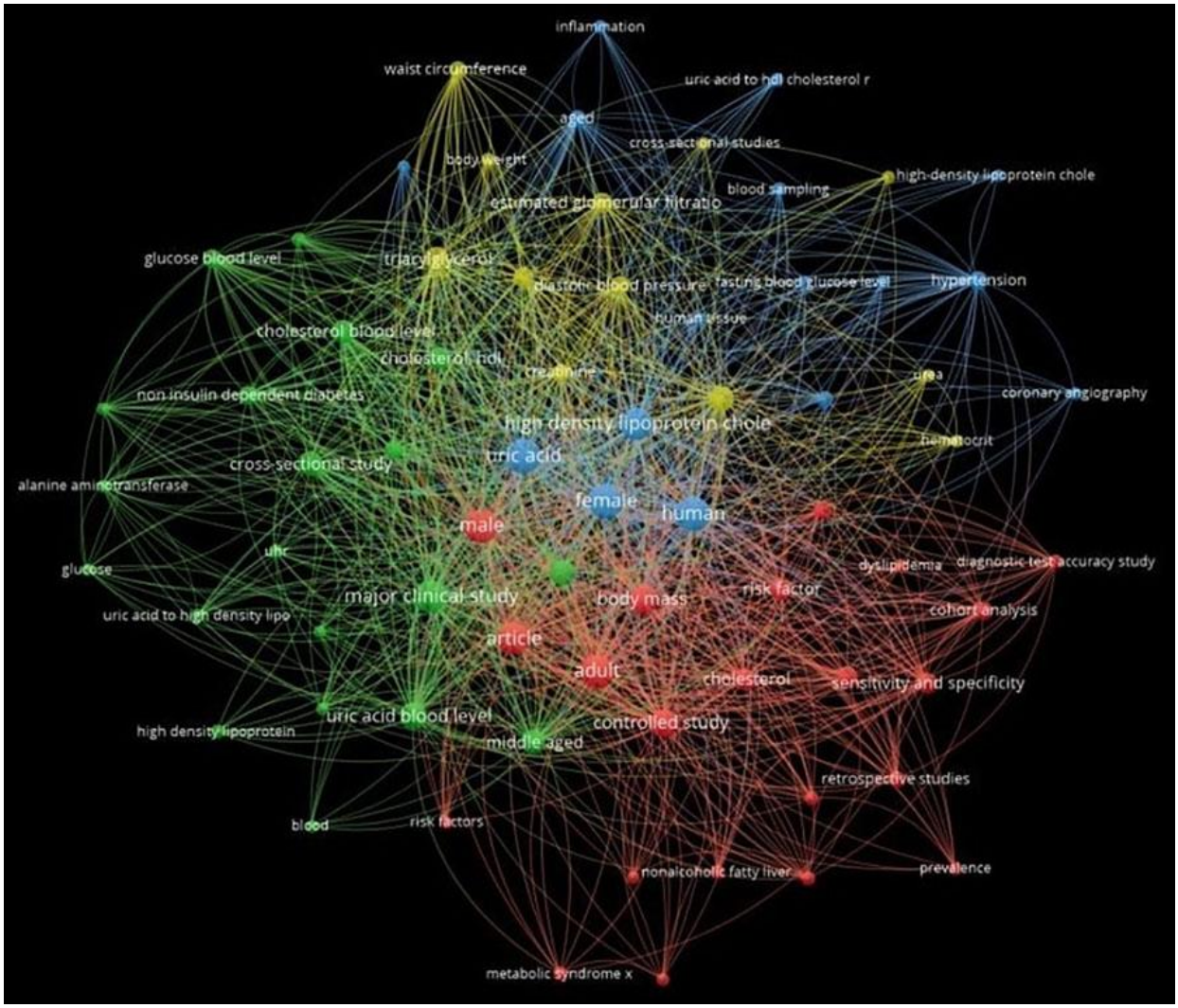

Figure 6. The co-occurrence view of the keywords

Discussion

In the present review, we provide a comprehensive examination of the current literature up to December 2023 regarding the relationship between UHR levels, as an emerging inflammatory biomarker, and various clinical conditions. At the time of writing this overview, no review article has been analyzed the existing research on UHR with a bibliometric analysis and highlighted its potential significance in clinical practice.

The UHR offers valuable insights into chronic inflammation and metabolic status. While hs-CRP and other pro-inflammatory cytokines such as IL-1 and IL-6 provide direct evidence of ongoing inflammation, UHR combines metabolic health and lipid status with inflammatory implications, may offer a broader perspective on cardiovascular risk. The dual nature of this biomarker facilitates a deeper understanding of the interplay between

lipid metabolism and inflammatory processes, which are crucial in the pathogenesis of the above-mentioned diseases. By leveraging UHR as a predictive tool, healthcare professionals may be better equipped to identify high-risk populations. This can pave the way for the development of targeted preventive strategies aimed at reducing the burden of chronic illnesses associated with inflammation and metabolic dysregulation. Overall, our review underscores the potential of UHR not only as a diagnostic marker but also as a strategic element in public health approaches to mitigate the risks of various clinical conditions. UHR is also a relevant and potentially informative measure in anthropometric studies across these specified populations. In the non-obese population, elevated in UHR levels might indicate early metabolic alterations and UHR monitoring may help identify individuals who are metabolically unhealthy despite having a normal weight. For overweight and obese individuals, the UHR may serve as a useful marker for assessing the risk of developing cardio-metabolic disorders; and elevated UHR may signal the need for lifestyle modifications or more aggressive management of cardio-metabolic risk factors.

While the UHR has consistently demonstrated a positive and independent correlation with various disorders, including CVDs, HTN, T2DM, and NAFLD, the question remains: can it serve as an alternative to traditional inflammatory markers in clinical practice? Furthermore, can UHR be reasonably utilized as a future predictor for these diseases?

It's important to recognize that a marker may statistically correlate with the presence of a disease, yet not play a significant role in the disease's causal pathway, potentially involving only a small proportion of the underlying pathophysiology (80). Therefore, while UHR may show associations, its utility in clinical decision-making should be approached with caution. For a biomarker to be ideal for use in clinical settings, it should not only correlate with disease presence but also contribute meaningfully to understanding disease mechanisms and guiding treatment decisions (81). Moreover, as UHR is a newly proposed inflammatory indicator, additional studies are requisite to discover its predictive ability in the development and the progression of diseases.

The results of the bibliometric analysis revealed an upward trend from 2020 in the annual number of publications, showing significant attention to different aspects of UHR in recent years. Also, most of the investigations about the use of the UHR in cardio-metabolic and CVDs have been conducted in China and Turkey. This can be attributed to several factors. Both China and Turkey face significant public health challenges related to cardio-metabolic disorders such as MetS and T2DM, which are related to elevated UA and dyslipidemia (82-85). Researchers in these countries may focus on inflammatory markers to better understand and manage these health concerns. Another factor to consider is the prevalence of UA levels, particularly hyperuricemia, which has been documented in specific populations within China and Turkey (86, 87), making these populations of particular interest for such studies. Furthermore, large databases and health surveys, particularly in China, may facilitate the collection of relevant data, thereby enabling researchers more thoroughly to explore relationships between UHR and health outcomes more effectively.

Given this information about UA and HDL-C, the UHR may serve as a valuable indicator of the interplay between inflammatory and anti-inflammatory states. UHR values could provide insights into the risk of associated disorders, even within the normal ranges of serum UA or HDL-C. This suggests that UHR could be a useful tool for assessing cardiovascular and metabolic health beyond traditional lipid measurements.

Strengths and limitations

The present overview was conducted to systematically cover the current researches regarding the relationship of UHR with cardio-metabolic disorders and CVDs with respect to the UHR's clinical landscapes and limitations. Until the time of writing this article, no comprehensive review article has been previously published in this field, which constitutes a significant strength of this study. Nonetheless, there are certain limitations to consider. Firstly, only 27 publications were included, representing a relatively small sample size. Secondly, the majority of the studies were conducted in just two countries (China and Turkey) which hinder this study to determine whether regional variations exist in the relationship between the UHR and cardio-metabolic disorders CVDs within the global population. Also, the bibliometric analysis predominantly focuses on publication trends, country and year of publication, and keywords co-accordance, which do not necessarily reflect the quality or clinical significance of the individual studies included. Moreover, as the included studies were heterogeneous in study design, population characteristics, and measurement methods, the generalizability of the conclusions regarding the role of the UHR in inflammatory cardio-metabolic

disorders may be affected. We suggest an ongoing surveillance of new relevant literature, utilizing multiple databases, and periodically update the bibliometric analysis to keep the review current and comprehensive.

Conclusion

The UHR represents a useful and easily accessible marker that may enhance our understanding of medical knowledge and improve clinical practice, independent of traditional risk factors. The coexistence of upraised serum UA and reduced HDL-C creates a synergistic effect, offering a more comprehensive assessment of inflammation and metabolic status. This combination can provide valuable insights for risk stratification, potentially identifying individuals at greater risk for associated conditions. However, due to the cross-sectional design of most investigations, UHR currently fails to have promising predictive ability. To fully understand the mechanisms underlying the association between UHR and cardio-metabolic disorders and also establish the predictive ability of UHR, further investigations are needed. Continued research in this area could lead to enhanced preventative and therapeutic strategies aimed at reducing disease burden and improving patient outcomes.

Declarations

Ethics approval and consent to participate

This study did not involve human participants or animals, and therefore, ethical approval and consent to participate was not required.

Consent for publication

Not applicable.

Availability of data and materials

This is a review article and does not contain any original data.

Competing interests

The authors declare that they have no competing interests related to this study.

Authors' contributions

Conceptualization: RKA; Searching articles and writing – original draft: RKA, AGH; Writing – review & editing: RKA, ARB; Visualization: AGH. All authors have read and approved the manuscript.

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Not applicable.

Declaration of Conflicting Interests

The authors declare no conflicts of interest related to this publication.

List of abbreviations

DM: diabetes mellitus; **HTN:** hypertension; **IR:** insulin resistance; **NAFLD:** non-alcoholic fatty liver disease; **CVDs:** cardiovascular diseases; **CRP:** C-reactive protein; **IL:** interleukin; **UA:** uric acid; **HDL-C:** high-density lipoprotein cholesterol; **UHR:** serum UA to HDL-C ratio; **T2DM:** type 2 DM (T2DM); **AUC:** area under the curve; **MetS:** metabolic syndrome; **FBG:** fasting blood glucose; **HbA1c:** glycosylated hemoglobin A1c; **BMI:** body mass index; **GFR:** glomerular filtration rate; **VFA:** visceral fat area; **DPDN:** diabetic peripheral distal neuropathy; **CKD:** chronic kidney disease; **DR:** diabetic retinopathy; **DKD:** diabetic kidney disease; **HOMA-IR:** homeostasis model assessment for insulin resistance; **VCTE:** vibration controlled transient elastography; **CABG:** coronary artery bypass graft surgery; **FFR:** fractional flow reserve; **NF-κB:** nuclear factor kappa B; **NO:** nitric oxide; **FABP3:** fatty acid-binding protein 3.

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