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ORIGINAL ARTICLE

Uric acid is a biomarker for heart failure, but not therapeutic target: result from a comprehensive meta-analysis

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Abstract

Aims This systematic review and meta-analysis aimed to investigate the association between serum uric acid (SUA) levels and the incidence rate and prognosis of heart failure (HF), as well as the impact of uric acid-lowering treatment on HF patients.
Methods and results PubMed and Embase were searched for original articles reporting on the association between SUA and HF incidence, adverse outcomes, and the effect of uric acid-lowering treatment in HF patients. Data were pooled using random effects or fixed effects models. Univariable meta-regression analysis assessed the influence of study characteristics on research outcomes. Statistical analyses were conducted using RevMan software and STATA software version 15.0. Eleven studies on HF incidence and 24 studies on adverse outcomes in HF patients were included. Higher SUA levels were associated with an increased risk of HF (RR: 1.81, 95% CI: 1.53–2.16), all-cause mortality (RR: 1.44, 95% CI: 1.25–1.66), cardiac death (RR: 1.56, 95% CI: 1.32–1.84), and HF rehospitalization (RR: 2.07, 95% CI: 1.37–3.13) in HF patients. Uric acid-lowering treatment was found to increase all-cause mortality in HF patients (RR: 1.15, 95% CI: 1.05–1.25).
Conclusions Uric acid is an independent predictor of heart failure occurrence and adverse prognosis. Targeting uric acid lowering as a therapeutic intervention does not improve the prognosis of patients with heart failure. It may not be advisable to use traditional urate-lowering drugs in young patients with heart failure, and elderly patients should exercise caution when using them.

Keywords Heart failure; Meta-analysis; Serum uric acid; Systematic review; Uric acid-lowering therapy

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Introduction

Over the past three decades, heart failure has emerged as a significant public health issue in both developing and developed countries.[1–3] The incidence and prevalence rates of heart failure increase with age.[4] Despite advancements in available therapies, patients with heart failure continue to experience high levels of morbidity and mortality.

Uric acid is the end-product of purine metabolism in the human body[5]; it is an antioxidant,[6] and it also has cardiovascular protective effects. There are several possible contributors to increased levels of UA in heart failure. Xanthine oxidoreductase (XO) is a catalytic enzyme in the process of purine metabolism. Under the action of this enzyme, xanthine is metabolized to generate UA, which produces reactive oxygen species (ROS). ROS can lead to various cardiovascular diseases, such as atherosclerosis, cardiac hypertrophy, myocardial fibrosis, left ventricular remodelling, and aggravated heart failure.[7,8] Reduced renal excretion and diuretic therapy can also lead to elevated levels of UA.[9,10] Numerous recent studies have established a close association between uric acid and the incidence and progression of heart failure.[11–13] This prompts questions regarding whether higher serum uric acid levels indicate a dysregulated pathway in the context of heart failure and whether lowering uric acid through treatment can improve adverse outcomes. The effectiveness of uric

acid-lowering treatment on heart failure outcomes remains controversial, with some studies suggesting its potential to improve adverse outcomes,[14–16] while others indicate no significant improvement in patient survival.[17–21]

Given the emergence of new studies, a comprehensive systematic review and meta-analysis are necessary to elucidate the relationship between serum uric acid, the incidence and prognosis of heart failure, and the impact of uric acid-lowering treatment on heart failure prognosis.

Methods

Data sources and searches

This systematic review and meta-analysis were performed following the PRISMA statement.[22] The research was registered with PROSPERO (CRD42023400927). To identify the published clinical studies that involved the relation of uric acid and the incidence of heart failure, the effect of uric acid on the prognosis of heart failure, and the impact of uric acid-lowering therapy on the prognosis of heart failure, we performed a comprehensive online search of the literature through the Medline and Embase databases (to May 2023), without language restriction. The retrieval strategy used relevant keywords and medical subject heading terms including the following: (uric acid) OR (uric acid) OR (urate) OR (serum uric acid) OR (SUA) AND (heart failure) OR (heart failure) OR (cardiac failure) OR (myocardial failure) OR (left ventricular dysfunction) OR (right ventricular dysfunction). The references of the reviewed manuscripts were manually retrieved to avoid missing relevant data.

Inclusion and exclusion criteria

The inclusion criteria for the association between uric acid and incidence rate and prognosis of heart failure were (i) prospective cohort studies, retrospective cohort studies, and case–control studies; (ii) assessing ≥1 of the following outcome measures: all-cause mortality and cardiovascular mortality, HF hospitalization, and the incidence rates of heart failure; (iii) endpoints were reported as numerical events rather than only hazard ratios, relative risk, or odds rate.[3] The definition of HF was based on physical signs, clinical symptoms, and therapeutic response.

The inclusion criteria for the association between ULT and outcomes of HF were (i) observational, cross-sectional studies, and randomized control trials; (ii) including patients with heart failure receiving uric acid lowering therapies; (iii) assessing ≥1 of the following outcome measures: all-cause mortality and cardiovascular mortality, HF hospitalization.[4] endpoints were reported as numerical events rather than only hazard ratios, relative risk, or odds rate.[5] The definition of HF was based on physical signs, clinical symptoms, and therapeutic response.

If related data were not reported in the published articles, we tried to contact the corresponding authors to get relevant information. We excluded multiple studies on the same population. Studies that reported inadequate details were also deleted unless we were able to retrieve the original data.

Study selection process

Two reviewers independently evaluated the records identified from the search for eligibility. The retrieval process consists of four stages. In the first stage, we screened the titles and abstracts to exclude the literature that did not meet the inclusion criteria. In the second stage, the full text of articles identified by two searchers as potentially relevant to the purpose of the study was obtained, and eligible articles were independently reviewed by two researchers. In the third stage, any disagreements regarding inclusion and exclusion were adjudicated by discussion or consultation with a third investigator. In the fourth stage, references of included studies were manually searched to identify any missed articles.

Data extraction and quality assessment

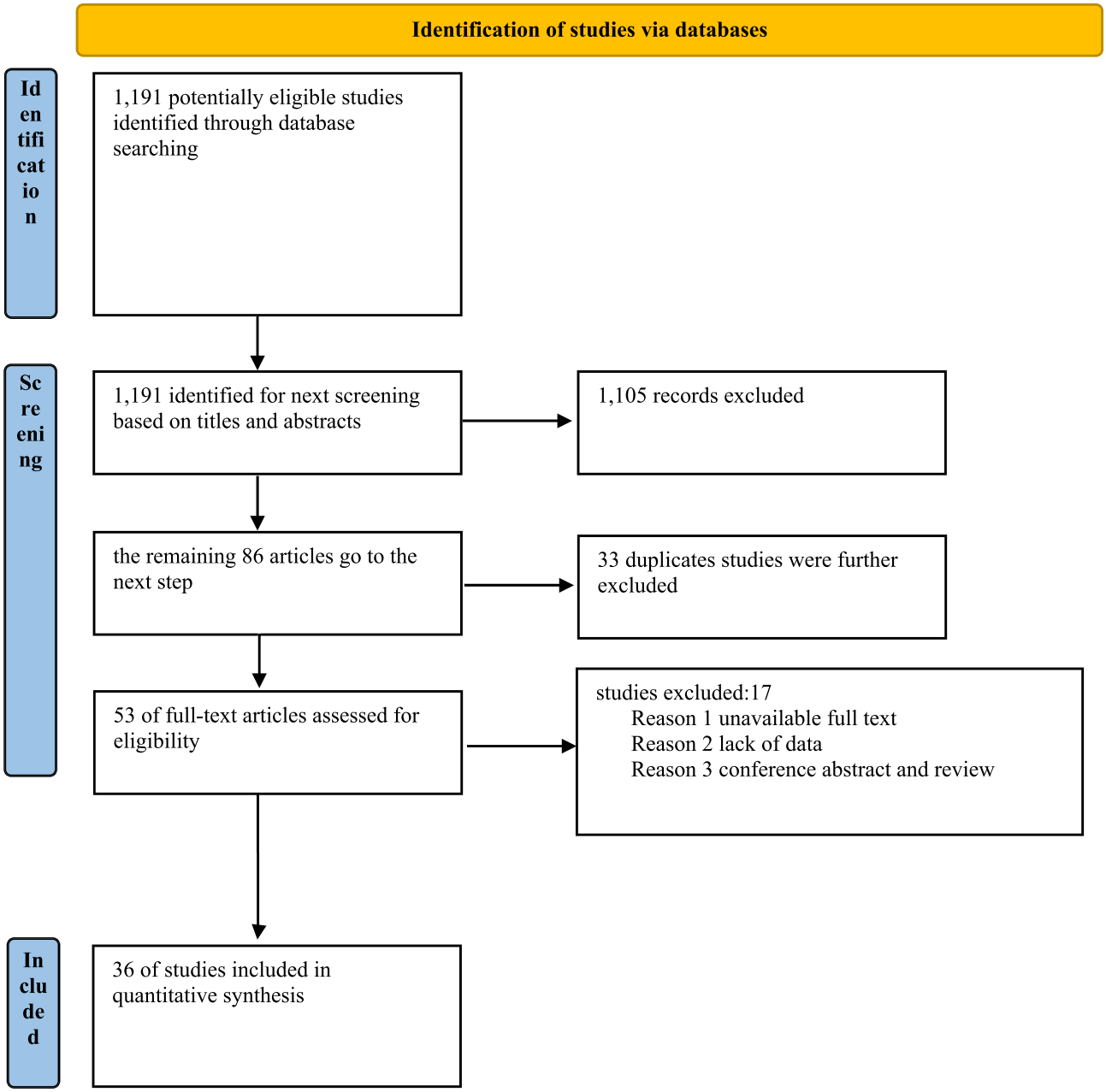
The preparation of data extraction and presentation of this manuscript followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Two authors conduct the data extraction through using a predefined, standardized protocol, and data collection instrument. The following data were extracted: study region, duration of the trial, publication data, sample size, baseline characteristics, intervention, and control. The Newcastle–Ottawa Quality Assessment Scale for observational trials was used to evaluate the quality of the included studies.[23] The randomized control trials were evaluated through the Cochrane Collaboration tool for assessing the risk of bias.

Date synthesis and analysis

This article is mainly a prognostic study, all outcome variables are dichotomous variables. This meta-analysis was conducted using the Cochran Mantel–Haenszel test under the random effect model to generate pooled risk ratio (RR) for the endpoints. Statistical heterogeneity within the studies was estimated using the I^2 statistic, and very low, low, moderate, and high levels of heterogeneity were defined as ≤25%, 25% to ≤50%, 50% to ≤75%, and ≥75%, respectively. For the primary outcomes, to inspect the impact of any single study on the pooling summary, sensitivity analysis was conducted by iteratively removing individual studies at each turn.

Multiple subgroup analyses (according to region, study design, publication year, sample size, and age of patients) were performed to further test the stability of our meta-analysis. To examine the source of heterogeneity, we performed a random-effects meta-regression analysis. The logarithm of RR for the endpoints was regressed against age, sample size, duration of follow-up, publication year, left ventricular ejection fraction, diabetes mellitus, and hypertension. It was weighted by the inverse variance of each study. To inspect any publication bias in the primary endpoints, we examined funnel plots for asymmetry in detail and evaluated them further using Egger regression asymmetry tests. The RevMan software package (Review Manager, Version 5.4) and STATA software 15.0 were used to perform all statistical analyses. An alpha criterion of P value <0.05 was considered statistically significant.

Figure 1 PRISMA 2020 flow diagram for new systematic reviews, including searches of databases and registries.



Results

Characteristics of included studies

Figure 1 displays the literature selection process. Initially, our search strategy identified a total of 1191 relevant studies, of which 1105 were excluded based on the evaluation of the title and abstract. We further excluded 33 duplicate studies. We conducted a full-text review of 53 studies to determine the eligible studies, and 17 studies were further removed for the following reasons: unavailable full text, lack of data, conference abstract, and review. Finally, 36 studies were included for further analysis (*Figure 1*). Among them, there were 11 studies on the association between uric acid and the incidence of HF, 10 studies on the association between uric acid and the prognosis of HF, and 14 studies on the association between uric acid lowering treatment and the adverse outcomes of HF.

Table 1 summarized the main patients characteristic of the 11 studies on the relation between uric acid and incident HF. A total of 438 296 patients were identified and analysed, with the median age of the subjects ranged from 36 to 73. The sample size varies from 216 to 353 613. Follow-up time ranged from 1 to 29 years. These studies were conducted in China,[24–26] Poland,[27] Italy,[28] Japan,[29] USA,[30–32] Turkey,[33] and Korea.[34] Heart failure was diagnosed according to ESC guidelines or based on symptoms, physical signs, and treatment response.

Table 2 summarized the main features of included studies on the association between uric acid and heart failure outcomes. A total of 16 742 patients were included, and the sample size vary from 102 to 4795. Follow-up time ranged from 0.8 to 6.3 years, these studies were conducted in China,[35,36] USA,[37,38] Turkey,[39] Canada,[38] and Japan.[40–44] In addition, there was one international multicentre study.[45] They were all cohort studies. Ten studies focused on the outcomes of all-cause mortality, eight studies on HF rehospitalization, and five studies were on cardiac death. The baseline proportion of diabetes and hypertension was also presented.

Table 3 summarized the baseline patient characteristic of 10 studies on the association between ULT and the prognosis of heart failure. A total of 19 294 patients were identified and analysed. Ten of the studies used traditional uric acid-lowering drugs like XOIs and uricosuric drugs, while four studies used novel uric acid-lowering drugs like sodium-glucose cotransporter 2 inhibiter (SGLT2i) and angiotensin receptor-neprilysin inhibitor (ARNi). The median age of the subjects ranged from 51.9 to 75 years, with a sample size ranging from 125 to 6204. Follow-up time range from 0.5 to 4.8 years. Two studies were from the USA,[17,21] two studies were from the Czech Republic,[16,46] one study was from Japan,[43] two studies were from the UK,[15,47] and the others were from China,[19] Canada,[48] Israel,[14] and Italy,[49] respectively. Additionally, there were three international multicentre studies.[50–52] Four were RCT studies, and the rest were all cohort studies.

Association between serum uric acid and incidence of heart failure

A total of 11 studies with 434 865 patients reported the incidence of heart failure. Pooled analysis with estimates as categorical variables showed the association between the higher uric acid group and the incidence of heart failure (RR: 1.81, 95% CI: 1.53–2.16) (*Figure 2*). There was a distinct statistical heterogeneity within the studies (I^2 = 90.0%, $P < 0.001$) (*Figure 2*). We performed meta-regression including gender, mean age, mean follow-up time, percentage of hypertension, diabetes mellitus, coronary artery disease, and body mass index as covariables, and the results showed that they all had no statistical significance ($P > 0.05$) (*Table* S2); therefore, these covariables were not the primary source of heterogeneity. The pooled analysis of the two studies with the largest sample size showed that the odds of incidence of heart failure in the higher uric acid group increased by 32% and with a slight degree of heterogeneity (I^2 = 32%, P = 0.21) (*Figure S2*). The results of sensitivity analysis showed that

Table 1 Baseline characteristics of included studies on the association between serum uric acid and incidence of heart failure

Reference	Year	Study design	Sample size (%male)	Region	Age (year)	Definition of higher UA (mg/dL)	Follow-up (year)	Quality score
Wu	2020	Cohort	2749 (55.0%)	China	70.9	Male 7.0, women 6.0	4	5
Liu	2021	Cross-sectional	216 (20.1%)	China	64.4	6.4	NR	7
Wełnicki	2022	Cross-sectional	829 (55.8%)	Poland	72.7	6.4	NR	6
Rebora	2022	Cross-sectional	1269 (73.7%)	Italy	68.0	Male 7.0, women 6.0	NR	7
Seki	2021	Cohort	353 613 (57.1%)	Japan	40.0	5.7	3.2	6
Gu	2018	Cohort	1009 (56.1%)	China	66.1	6.2	7.2	6
Essex	2017	Cohort	65 329 (69.4%)	USA	63.7	6.0	1.0	7
Kaya	2012	Cohort	2249 (80.5%)	Turkey	58.2	Male 7.0, women 6.0	2.0	6
Ekundayo	2010	Cohort	5461 (44.0%)	USA	73.0	Male 7.0, women 6.0	8.1	6
Krishnan	2009	Cohort	4912 (47.0%)	USA	36.0	6.2	29.0	8
Bae	2007	Cohort	660(59.0%)	Korea	59.2	5.7	2.3	7

NR, not reported; UA, uric acid.

Table 2 Baseline characteristics of included studies on the association between uric acid and adverse outcomes of heart failure

References	Year	Age	Sample size (%male)	Study design	LVEF	HTN	DM	Country	Follow up(y)	Definition of higher UA level (mg/dL)	Reported primary outcomes	Quality score
Yılmaz	2022	64	861 (72.6%)	Cohort	30	53.2	38.6	Turkey	2.5	7	All-cause mortality HF rehospitalization	6
Wang	2022	61.1	102 (69.7%)	Cohort	31	21.9	14.1	China	2.8	7	All-cause mortality HF rehospitalization	6
Vaduganathan	2014	65.8	395 (74.4%)	Cohort	27.6	71	38.7	USA	0.8	8.8	All-cause mortality Cardiac death HF rehospitalization	7
Filippatos	2021	61	2645 (79.0%)	Cohort	23	59	35.5	USA, Canada	2.1	Male 8, women 6	All-cause mortality Cardiac death HF rehospitalization	7
Fujihashi	2021	69.1	4652 (65.4%)	Cohort	55.5	87.8	39	Japan	6.3	9.2	All-cause mortality HF rehospitalization	7
Zhou	2019	66.0	535 (63.6%)	Cohort	48.6	25.8	28.6	China	1.8	7	All-cause mortality	8
Hamaguchi	2011	71.1	1869 (60.2%)	Cohort	44.5	53.4	31.6	Japan	2.1	7.4	All-cause mortality Cardiac death HF rehospitalization	6
Selvaraj	2020	72.9	4795 (48.4%)	Cohort	58	95.5	44.4	Multiple country	NR	NR	All-cause mortality Cardiac death HF rehospitalization	7
Shimizu	2015	68.1	424 (48.6%)	Cohort	61.1	75	32.5	Japan	2.5	7	All-cause mortality Cardiac death	5
Nishino	2022	82.5	464 (49.8%)	Cohort	60.5	88	33.4	Japan	1.3	8.3	All-cause mortality HF rehospitalization	6
Ambrosio	2021	64.6	4938 (72.1%)	Cohort	37.5	7.9	34.3	Italy	1.5	6.6	Cardiac death HF rehospitalization	7
Niizeki	2006	77.5	123 (NA)	Cohort	49.7	54.7	19.5	Japan	1.2	6.5	Cardiac death HF rehospitalization	6

DM, mellitus diabetes; HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fractional; NA, not available.

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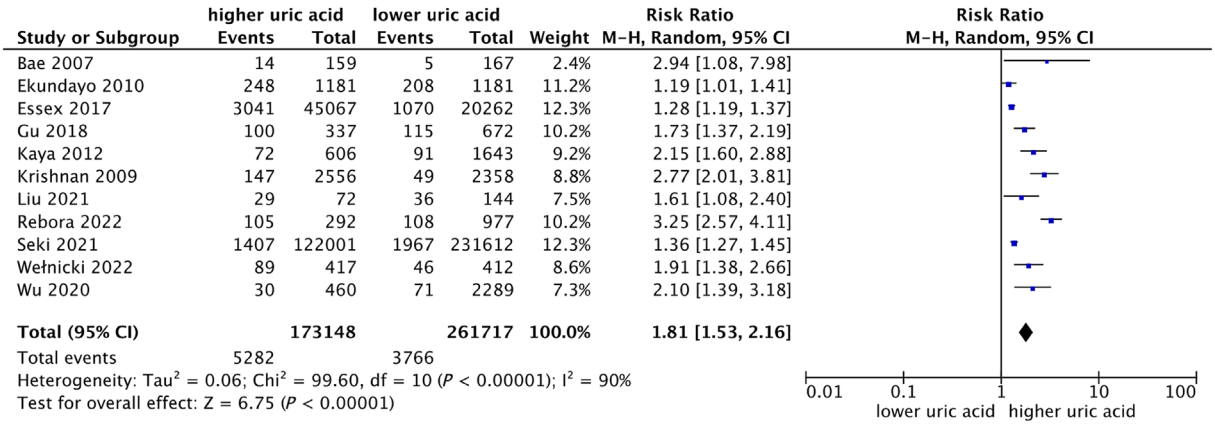
Table 3 Baseline characteristics of the included studies on the association between ULT and the adverse outcomes of heart failure

References	Year	Country	Study design	Sample size	Age (year)	Follow-up (year)	Reported primary outcomes	NOS points
Givertz	2015	USA	RCT	253	63	0.5	All-cause mortality Cardiac death CV rehospitalization	RCT
Hare	2008	Canada	RCT	405	64.5	0.5	All-cause mortality Cardiac death CV rehospitalization	RCT
Pavlusova	2019	Czech Republic	Cohort	3160	73	5	All-cause mortality	7
Málek	2012	Czech Republic	Cohort	1159	73.4	1	All-cause mortality	6
Xiao	2016	China	RCT	125	51.9	0.8	All-cause mortality Cardiac death CV rehospitalization	RCT
Gotsman	2012	Israel	Cohort	6204	75	1.4	All-cause mortality	7
Wu	2010	USA	Cohort	1152	64.8	1.5	All-cause mortality	7
Wei	2009	UK	Cohort	4785	71.9	4.8	All-cause mortality Cardiac death CV rehospitalization	6
Struthers	2002	UK	Cohort	1760	66.9	4	All-cause mortality Cardiac death CV rehospitalization	4
Nishino	2022	Japan	Cohort	291	81.5	1.3	All-cause mortality CV rehospitalization	6
McDowell	2022	Multiple countries	RCT	253	67.3	1	All-cause mortality	RCT
Doehner	2022	Multiple countries	RCT	405	66.8	NR	All-cause mortality Cardiac death	RCT
Mazza	2020	Italy	RCT	3160	78.6	1	All-cause mortality CV rehospitalization	RCT
McMurray	2014	Multiple countries	RCT	1159	63.8	2.3	All-cause mortality Cardiac death CV rehospitalization	RCT

NOS, Newcastle–Ottawa Quality Assessment Scale; RCT, randomized controlled trials.

Figure 2 Forest plot of association between uric acid and incidence rate of heart failure.



there was no significant change in the effect size when we removed any of the studies (*Figure S3*), which suggested that our results were stable. We also conducted subgroup analyses according to publication year, sample size, and ethnicity, and all subsets consistently showed that hyperuricaemia was strongly associated with an increased risk of suffering from HF (*Table S3*). There was obvious publications bias based on funnel plot and Egger's test (*Figure S4*).

Relations of serum uric acid and adverse outcomes among patients with heart failure

We included all studies that reported all-cause mortality by categorical uric acid levels, and as shown in *Figure 3*, elevated serum uric acid levels were associated with a significantly increased risk of all-cause mortality (RR: 1.44, 95% CI: 1.25–1.66) in a random-effect model, with appreciable

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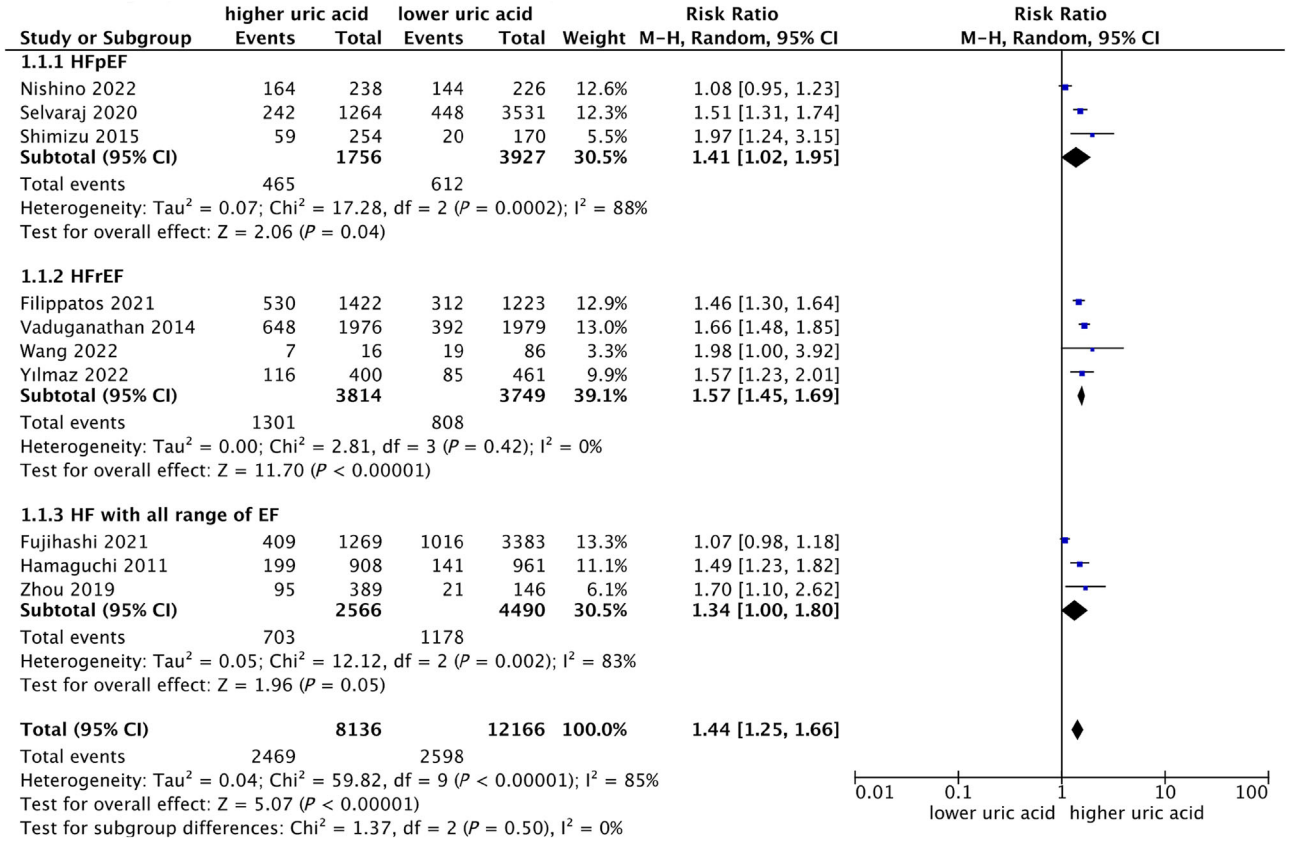
Figure 3 Forest plot of association between uric acid and all-cause mortality of heart failure.



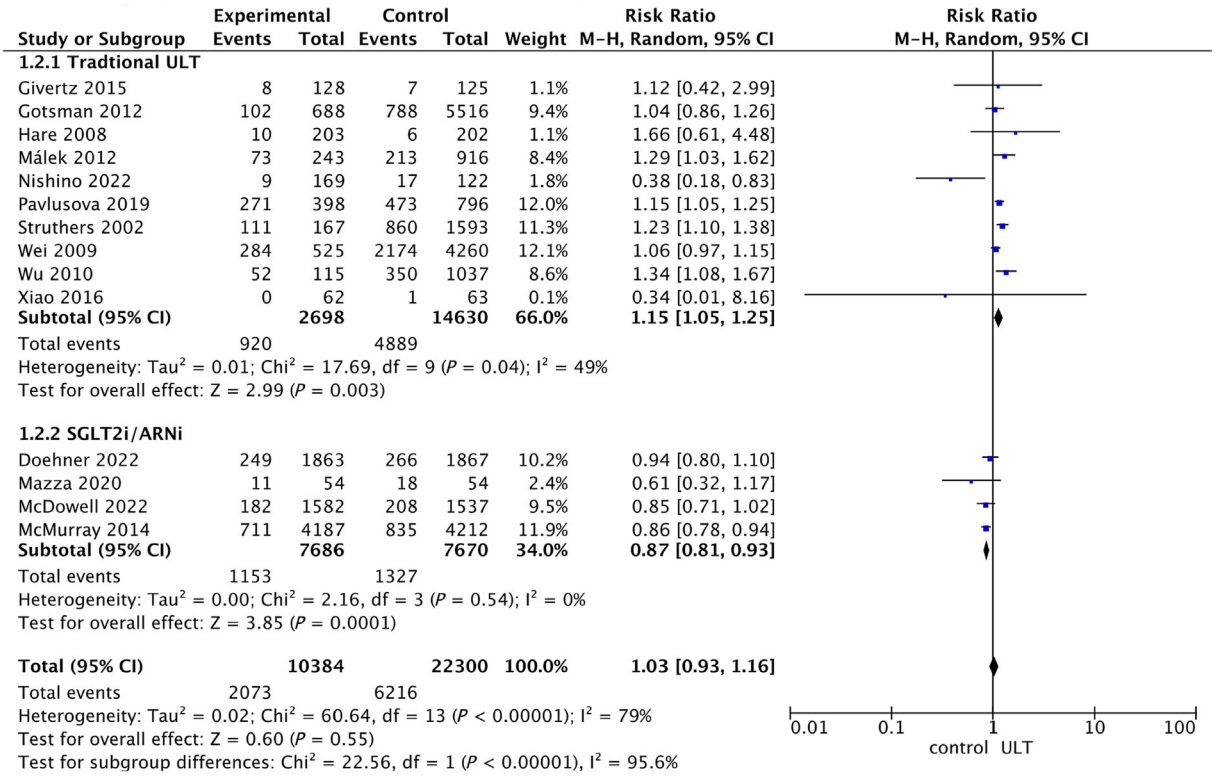
heterogeneity (I^2 = 85.0%, $P < 0.001$) (*Figure 3*). Among these studies, three studies are HF with reduced EF and three studies were HF with preserved EF, with higher UA group led to 41% (RR: 1.41, 95%: 1.02–1.95) and 57% (RR: 1.57, 95%: 1.45–1.69) increases in the risk of all-cause mortality in heart failure with preserved ejection fraction and heart failure with reduced ejection fraction, respectively (*Figure 3*). Sensitivity analysis indicated that none of the studies significantly influence the overall pooled risk summary (*Figure S5*). Meta-regression suggested that no significant correlation between the preselected covariables and the all-cause mortality was observed (*Table S4*). Subgroup analyses showed that in each subset, their effect sizes were significant (*Table S5*). No publication bias was found for the pooled all-cause mortality of heart failure based on the funnel plot and Egger's test (*Figure S6*).

Of the 10 studies we included, seven studies reported the outcome of cardiovascular death, and seven studies reported the outcome of HF rehospitalization. They also suggested that hyperuricaemia was associated with an increased risk of cardiovascular death and HF hospitalization (cardiovascular death, RR: 1.56, 95% CI: 1.32–1.84; HF rehospitalization, RR: 2.07, 95% CI: 1.37–3.13) (*Figures S7* and *S8*).

Effect of lowering uric acid on cardiovascular outcome in patients with heart failure

We included 14 studies involving 32 684 patents on uric acid-lowering therapy for patients with heart failure, 10 of which were traditional uric acid-lowering drugs, including XOI and uricosuric drugs, and four were novel uric acid-lowering drugs, such as SGLT2i and ARNi. A pooled analysis of traditional urate-lowering drugs showed that lowering uric acid treatment was associated with an increased risk of all-cause mortality (RR: 1.15, 95% CI: 1.05–1.25) (*Figure 4*), with a moderate heterogeneity (I^2 = 49.0%) (*Figure 4*). In contrast, novel urate-lowering drugs were associated with reduced all-cause mortality in heart failure patients (RR: 0.87, 95% CI: 0.81–0.93) (*Figure 4*). To explore the heterogeneity of the studies, a subgroup analysis on all-cause mortality was performed by ethnicity, study design, publication date, type of heart failure, and sample size. Apart from Asia and RCT did not reach statistical significance, the rest of the subsets showed that in HF patients, elevated UA level was associated with an increased risk of all-cause mortality (*Table S6*). By univariate meta-regression analysis (*Table S7*), we found a

Figure 4 Forest plot of association between uric acid-lowering therapy and all-cause mortality of heart failure.



trend that the risk of all-cause mortality in patients with heart failure who received urate-lowering therapy gradually decreased with increasing age (P = 0.07) (*Figure 5*). We divided the age into two subgroups with 70 years old as the cutoff, and we found that among those younger than 70 years old, ULT was not associated with all-cause mortality in patients with HF (RR: 1.09, 95% CI: 0.97–1.23), whereas in people older than 70 years, ULT is associated with all-cause mortality in HF patients (RR: 1.26, 95% CI: 1.14–1.41). When we remove any of the studies, the results of sensitivity analysis suggest that there is no significant change in the effect size, indicating that our results have stability (*Figure S9*). No visual publication bias was found based on the funnel plot (*Figure S10*).

Five studies reported cardiovascular mortality, and heart failure patients with lowering uric acid treatment were more susceptible to cardiovascular death (RR: 1.29, 95% CI: 1.04–1.26) with a substantial statistical heterogeneity (I^2 = 56.0%) (*Figure S11*). Five studies showed HF rehospitalization, and the pooled data from the five studies reported that the effect of uric acid-lowering therapy on cardiovascular hospitalization for heart failure patients did not reach statistical significance (RR: 1.09, 95% CI: 0.75–1.59) (*Figure S12*).

Discussion

Our systematic review and meta-analysis systematically elucidate the relationship between uric acid and the occurrence and development of heart failure. Our findings indicate that elevated serum uric acid levels are associated with an increased risk of heart failure occurrence and prognosis. Uric acid serves as a predictor of all-cause mortality, cardiovascular mortality, and HF rehospitalization in heart failure patients. However, it is important to note that reducing uric acid levels in heart failure patients does not improve long-term prognosis and may even increase all-cause mortality. Through meta-regression analysis, we observed that this impact gradually decreases with age.

Several previous meta-analyses have demonstrated the association between higher serum uric acid and the incidence and prognosis of HF. A meta-analysis, which included five studies, published by Huang et al., pointed out that hyperuricaemia was associated with an increased risk of suffering from HF (HR: 1.65, 95% CI: 1.41–1.94), for every 1 mg/dL increase in SUA, the odds of development of HF increased by 19% (HR: 1.19, 95% CI: 1.17–1.21).[12] In a meta-analysis published in 2021 by Miao et al., it was revealed that higher levels of serum uric acid are associated with an increased risk

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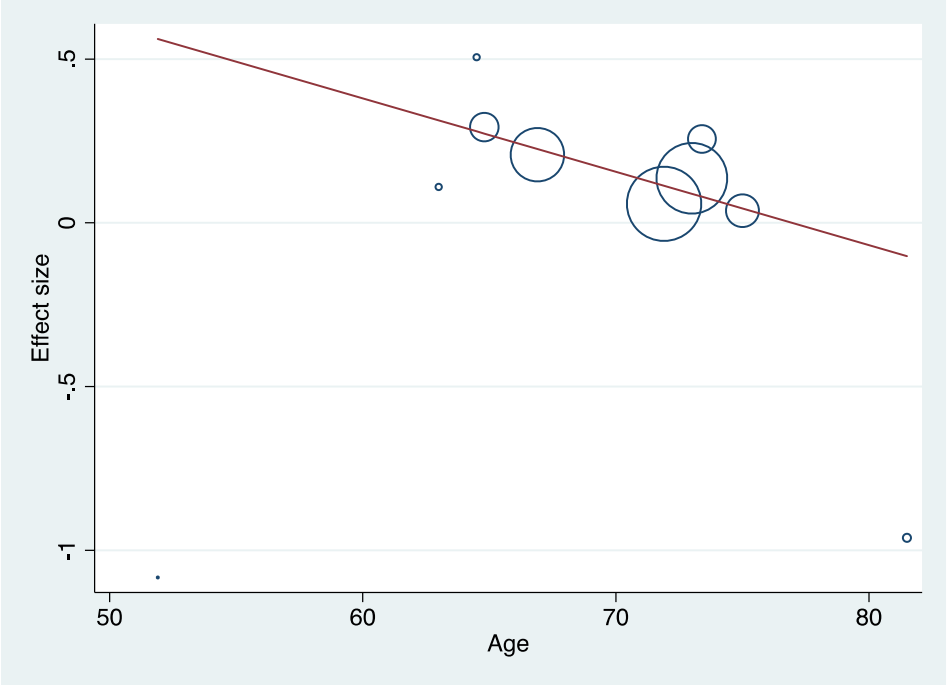
Figure 5 Univariate meta-regression analysis (age) of association between ULT and all-cause mortality of heart failure.



of all-cause mortality (HR: 2.24, 95% CI: 1.49–3.37), cardiovascular mortality (HR: 1.26, 95% CI: 1.06–1.23), and the composite of death or cardiac events (HR: 1.26, 95% CI: 1.01–1.56) in patients with chronic heart failure.[53,54] Additionally, Tamariz et al. found that patients with HF and hyperuricaemia (SUA $>$ 6.5 mg/dL) have an increased risk of death compared with those with normal uric acid levels. Huang et al. demonstrated that higher UA level independently predicts all-cause mortality and composite of readmission or death in acute heart failure patients.[53,54]

Although the specific pathological role of uric acid in the occurrence and development of HF is still not very clear, several speculations have been made: Hyperuricaemia has been associated with worse haemodynamic measures.[32] Functional upregulation of XO during purine metabolism can generate ROS and uric acid. ROS may contribute to the pathophysiological process of chronic heart failure, such as ventricular remodelling, myocardial fibrosis, cardiac hypertrophy, and impaired contractility.[55–58] Radovanovic et al. demonstrated that uric acid is associated with left ventricular remodelling in patients with chronic ischaemic.[59] Uric acid damages vascular endothelial cells and increases blood pressure, leading to a poor prognosis.[60–64] Additionally, in patients with heart failure, sympathetic nerve excitation results in the release of catecholamines, which constrict afferent arterioles, decreased glomerular filtration rate, decreased uric acid excretion, and increased blood uric acid concentration. Increased uric acid further activates the RAAS, leading to cardiac remodelling and poor prognosis.[32]

Compared with other cardiac-specific biomarkers, uric acid measurement has several advantages in assessing cardiovascular risk, heart-related mortality, and heart failure readmissions. These advantages include the routine availability of uric acid measurement as a standard biochemical test that can be easily performed by collecting blood samples. In comparison with other biomarkers, the process of uric acid testing is simpler and more feasible for implementation.[65] Uric acid levels can provide additional information to cardiac-specific biomarkers like BNP, NT-proBNP, and troponins. While BNP and NT-proBNP primarily reflect myocardial stretch and volume overload, and troponins indicate myocardial injury, uric acid reflects other aspects of HF pathophysiology, including vascular dysfunction and metabolic abnormalities. Combining multiple biomarkers, including uric acid, can provide a more comprehensive assessment of cardiovascular risk and prognosis.[66]

Therefore, uric acid-lowering therapy may be one of the potential targets for the treatment of heart failure. However, Kanbay et al. demonstrated that uric acid-lowering therapy was associated with increased all-cause mortality in heart failure patients (HR: 1.24, 95% CI: 1.04–1.49).[67] Similarly, in another meta-analysis of randomized controlled trials conducted by Xu et al., involving 864 elderly patients with heart failure, uric acid-lowering treatments did not show improvement

in brain natriuretic peptide, the 6-min walk test, left ventricular ejection fraction, cardiovascular death, and all-cause mortality. Our comprehensive meta-analysis consolidates previous findings and concludes that solely targeting uric acid-lowering treatment for heart failure does not improve prognosis, indicating that elevated uric acid levels serve only as a predictive factor for heart failure.

Through meta-regression analysis, we observed that younger patients were less responsive to traditional uric acid-lowering drugs, and the effect of uric acid-lowering therapy on the prognosis of heart failure would gradually decrease with increasing age. This phenomenon may be attributed to XO production of uric acid and generation of ROS, which have oxidative effects and can contribute to various cardiovascular diseases, including atherosclerosis, cardiac hypertrophy, myocardial fibrosis, left ventricular remodelling, and worsened heart failure. XO is upregulated within the heart in both experimental and human heart failure.[68] Thus, patients who are older and have a longer course of disease may have more XO in their hearts. Under such circumstances, the use of XOI may have a certain positive effect on prognosis, but this effect still cannot improve the prognosis of patients. Nevertheless, this is merely our speculation, and more experimental studies are needed to elucidate the specific mechanism. Research by Mazza et al. has shown that ARNi can improve UA levels in patients with heart failure with reduced ejection fraction, and a recent study by Butt et al. found that SGLT2i dapagliflozin had a urate-lowering effect and reduced the initiation of new treatments for hyperuricaemia and gout.[69] Our study also included two novel urate-lowering drugs. In contrast to traditional uric acid-lowering drugs, these medications have been shown to improve the prognosis of heart failure. We further analysed the reasons for this and found that these two medications are not specifically targeted at reducing uric acid. The mechanism by which they lower uric acid is as follows: SGLT2 inhibitors exert their effects by blocking glucose reabsorption, resulting in increased glucosuria and subsequent osmotic diuresis. This diuretic effect may lead to increased uric acid excretion and a subsequent reduction in serum uric acid levels. ARNi reduces the activity of the renin-angiotensin-aldosterone system by inhibiting angiotensin-converting enzyme and blocking the action of angiotensin II (Ang II), thereby reducing pressure in the glomerulus and improving uric acid excretion. These two drugs can improve heart failure, and the improvement of heart failure may also cause the reduction of uric acid. This may also be the reason why these two drugs have the opposite effect on the prognosis of heart failure compared with traditional urate-lowering drugs. These were just our speculations, and further studies were needed to clarify the specific mechanism.

While uric acid can be used as a biomarker for the occurrence and prognosis of heart failure, it cannot be used as a targeted drug for the treatment of heart failure. In patients with heart failure, there are many factors contributing to increased uric acid levels, such as the use of diuretics, the activation of XO, and the impairment of renal function. Simple uric-lowering therapy cannot improve the prognosis of patients with heart failure, and even increase the risk of death of patients.

To the best of our knowledge, this study is the first comprehensive meta-analysis to examine the impact of uric acid on the occurrence and prognosis of heart failure, as well as the effect of uric acid reduction on the prognosis of heart failure patients. Our meta-analysis revealed that UA is an independent predictor of all-cause mortality, CV death, or HF rehospitalization. The literature included in our meta-analysis is relatively comprehensive, with a large sample size, which provides a certain degree of reliability and stability to the results. However, several limitations should be acknowledged. Firstly, our meta-analysis exhibited significant heterogeneity, which could be attributed to differences in patient characteristics, treatments used, and follow-up durations among the included studies. Despite conducting subgroup and sensitivity analyses, the exact source of heterogeneity could not be identified. Secondly, individual studies have different thresholds for high or low uric acid, which might contribute to the relatively large heterogeneity observed in our results. Thirdly, the funnel plots for heart failure incidence and all-cause mortality displayed asymmetrical, suggesting a potential publication bias, possibly due to some small unpublished studies. We did not include conference proceedings, which might mean that we might miss some small, unpublished studies. Fourthly, UA levels in our included literature are all categorical variables, which may lead to biased results. Fifthly, although our findings suggest a decreased effectiveness of uric acid-lowering therapy on heart failure prognosis with increasing age, the *P*-value did not reach statistical significance ($P = 0.07$). Therefore, future studies involving patients with heart failure across a wider age range are necessary to strengthen this conclusion. Sixthly, for the first question, the results of all the studies are concordant, which tends to reduce the relevance of the meta-analytic assessment. Finally, due to inadequate data, the relationship between uric acid and different types of heart failure could not be assessed in our meta-analysis.

Conclusions

Uric acid is an independent predictor of heart failure occurrence and prognosis. Targeting uric acid lowering as a therapeutic intervention does not improve the prognosis of patients with heart failure. It may not be advisable to use traditional urate-lowering drugs in young patients with heart failure, and elderly patients should exercise caution when using them.

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Conflict of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. The literature search strategies.
Table S1. The quality assessment for literatures of observational studies.
Figure S1. The quality assessment for literatures of randomized controlled trials.
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Figure S11. Forest plot of association between uric acid-lowering therapy and cardiovascular death of heart failure.
Figure S12. Forest plot of association between uric acid-lowering therapy and HF rehospitalization of heart failure.

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