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Research Article

Efficacy and Safety of Topiroxostat in Patients with Chronic Kidney Disease and Hyperuricemia: A Meta-Analysis

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Abstract

Background and Objective: Hyperuricemia (HUA) and chronic renal disease occurrences have both been sharply increasing in recent years, which have seriously affected public health. This meta-analysis compares topiroxostat in patients with chronic kidney disease and hyperuricemia. **Materials and Methods:** The machine searches eight databases to find studies on topiroxostat's impact on individuals with chronic renal disease and HUA, both domestically and overseas. Utilising RevMan 5.3 software, data analysis was carried out following a thorough assessment of the quality of the literature. **Results:** A total of seven articles were included in this meta-analysis. All of them were thought of as controlled experiments. The test category's uric acid levels significantly changed from the control group (SMD: -2.12; 95% CI: -2.68, -1.56; $p < 0.01$), as per 4 studies. The Estimated Glomerular Filtration Rate (eGFR) (SMD: 0.62; 95% CI: -3.98, 5.23; $p = 0.790$), systolic blood pressure (SMD: -0.20; 95% CI: -5.23, 4.83; $p = 0.938$), diastolic blood pressure (SMD: -0.76; 95% CI: -4.42, 2.91, $p = 0.685$), urine protein positive rate (SMD: 0.55; 95% CI: 0.25, 1.22; $p = 0.143$) and ADR (SMD: 1.16; 95% CI: 0.78, 1.72; $p = 0.459$). **Conclusion:** According to current study findings, topiroxostat may be useful for treating HUA and chronic renal disease in individuals, as evidenced by uric acid. However, topiroxostat did not significantly improve the levels of eGFR, BP and protein-positive rate of urine and the above conclusions need to be verified by more high-quality studies.

Key words: Topiroxostat, chronic kidney disease, hyperuricemia, serum uric acid, systolic blood pressure, diastolic blood pressure, urine protein positive rate

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Long-term renal problems and hyperuricemia (HUA) have become more common in recent years, with serious consequences for public health. Chronic renal illness has been spreading rapidly around the globe in recent times¹. Early in the twenty-first century, a meta-analysis of the prevalence of chronic kidney illness in Chinese people was performed and revealed that the condition was prevalent in 13 Chinese provinces at a rate of roughly 12.8%, which was significantly higher than that in foreign countries². Even though the development of chronic kidney disease in women is more frequently delayed than in men, it may be related to men's poor diet and irregular work and rest³. The 2020 Global Kidney Disease Health Report shows that less than one-third of countries and regions have included chronic kidney disease in their priority treatment plans and only 24% of countries and regions have stipulated screening for the long-term disease of the kidney⁴. Chronic kidney disease develops slowly and is not well understood. The lack of education on chronic kidney disease in hospitals is inseparable⁵. Hyperuricemia (HUA), which refers to the excessive levels of uric acid in the blood, is widely recognised as the primary cause of gout. This condition occurs due to the buildup of uric acid crystals. In recent years, the frequency of HUA has increased and it is another high-incidence metabolic disease after hyperlipidemia⁶. Serum uric acid (UA) is linked to cardiovascular, renal and metabolic diseases, as well as its components, including high blood sugar, high levels of triglycerides and obesity⁷. Studies have shown that lipid is more strongly linked to UA than any other component of metabolic syndrome. However, the specific function of a particular lipid species on UA levels might vary across various populations⁸. Some researchers believe that excessive blood uric acid can activate the expression of the uric acid transporter in endothelial cells, increase oxidative stress and inflammatory responses, lead to endothelial cell damage and encourage the growth and incidence of chronic kidney illness^{9,10}. Endothelial cell dysfunction is also involved in the occurrence and development of arteriosclerosis, causing cardiovascular complications¹¹. The incidence of heart disease and all mortality in individuals with chronic renal disease has significantly increased¹². There is no similar evidence on non-dialysis individuals who have severe renal disease, but new studies have demonstrated that the inflammatory process and endothelial dysfunction in dialysis people ameliorate with uric acid-lowering medicine¹³. At present, the

commonly used drugs to inhibit the synthesis of uric acid are mainly XO inhibitors, including allopurinol, febuxostat and topiroxostat. However, allopurinol inhibits the formation of guanine and interferes with the metabolism of a pyrimidine to synthesise DNA, so there are more adverse reactions¹⁴. Febuxostat is a potent XO inhibitor. It can produce a strong XO inhibitory effect with a small dose and it does not interfere with the metabolism of purine and pyrimidine¹⁵. Therefore, it has fewer adverse reactions than allopurinol and is widely used today. As a novel XO inhibitor introduced in Japan in 2013, febuxostat excretes 49% of its body weight through the kidneys and the remaining 71% through the liver, while topiroxostat is completely metabolised in the liver and eliminated through the bile, not the liver¹⁶. Renal excretion will greatly reduce the burden on the kidneys, potentially making it more appropriate for gout sufferers with renal failure. Hence, this meta-analysis investigates the effectiveness of topiroxostat in individuals suffering from chronic renal diseases.

MATERIALS AND METHODS

Study area: The current investigation was conducted at the Department of Nephrology, First People's Hospital of Linping District, from June to August, 2023.

Study selection: Type of study design RCTs that have been published on the benefits of topiroxostat in individuals with HUA and chronic renal disease. However, the animal trials were excluded.

Participants selection: This study included only those who suffered from chronic kidney disease and HUA.

Intervention types: Topiroxostat used in conjunction with other treatments were given to individuals who had ongoing renal failure and HUA, while the placebo category got no treatment.

Types of outcome measures: Prognostic markers in people with HUA and chronic renal disease. The following are some assessment methods for using topiroxostat in combination with other therapies to treat chronic renal disease and HUA: (1) Uric acid, (2) eGFR, (3) Blood pressure, (4) Adverse reactions and (5) Urine protein positive rate. A minimum of one of the aforementioned scores was used in the literature used in this research to assess outcome measures.

Search strategy: The Cochrane Library, Web of Science, PubMed, Embase, China Biomedical Literature Database (CBM), VIP, CNKI and WanFang the computer retrieves info from all sources. Topiroxostat, chronic renal disease and HUA are the search terms. The inquiry was conducted from the beginning of the library until June, 2023. The methods for performing a literary search are as follows: (1) Look for relevant documentation in the Chinese and English databases; (2) Use "MeSH Terms" to find the subject terms in the English database search; (3) Search using a mix of subject words and keywords.

Extracting data and evaluating its quality: The literature screening procedure was carried out separately by 2 researchers after the initial screening of the summary. The findings of the literature screening were then acquired by perusing the entire text. Until the outcomes are agreed upon, exchange screening findings, talk about opposing literature or contact a third scholar. Basic details about the literature, study style, study object, sample size, intervention substance, outcome measures, etc., are among the information derived from the data.

Statistical analysis: This meta-analysis was performed using the Review Manager software (RevMan). (1) Results come together: This study's outcome measures were all quantified statistics that were evaluated utilising various instruments. Because there are variations in the scores, the standardised mean difference (SMD) and 95% (confidence interval, CI) are utilised as a measure of impact. (2) Test for homogeneity: Chi-square analyses are utilised to assess the degree of study variability, if $p > 0.1$, $I^2 \leq 50\%$, According to reports, the included research was more uniform. Implement a fixed-effects model. Meta-analyses; if $p < 0.1$, $I^2 > 50\%$, analyse heterogeneous resources, if there is no clinical heterogeneity, if heterogeneity was suggested in the included papers. Meta-analyses employ a random-effects approach. Subgroup analysis included a potential comparison of qualitative variables.

RESULTS

Search results: A total of 492 references were identified as a result of the search method used in the research. After removing identical investigations, 30 studies were scanned using the summary and title. The complete contents of ten pieces were then read. A comprehensive text analysis resulted in the elimination of 3 entries due to data discrepancy ($n = 2$) and absent data ($n = 1$), correspondingly. This meta-analysis ultimately would include 7 papers (Table 1). The PRISMA assertion flow graphic shows how to go about doing this (Fig. 1).

Uric acid: The uric acid levels of both the test group and the control category were recorded in four studies. The test group uric acid content was significantly lower compared to the control group, as per meta-analysis (SMD: -2.12; 95% CI: -2.68, -1.56; $p < 0.01$, Fig. 2). It was done to create a uric acid funnel chart (Fig. 3). Results from each of these trials were extremely diverse and a sensitivity analysis was conducted (Fig. 4). In comparison to the control population, topiroxostat lowers uric acid content in individuals with chronic renal illness and HUA.

eGFR: Two investigations examined the eGFR in both the diagnostic group and the reference team. The experimental group eGFR did not significantly vary from the control sample when compared to them (SMD: 0.62; 95% CI: -3.98, 5.23; $p = 0.790$, Fig. 5). All of these studies' results had low variability and a sensitivity analysis was done (Fig. 6).

Systolic blood pressure: The systolic blood pressure of the testing sample and the control groups was reported in 2 trials. The diastolic pressure of the experimental category did not vary significantly from that of the control cohort, according to a meta-analysis (SMD: -0.20; 95% CI: -5.23, 4.83; $p = 0.938$, Fig. 7). The results of all of these studies showed low variability and a sensitivity analysis was conducted (Fig. 8).

Table 1: Basic characteristics of the included studies

Study	Sample size (T/C)	Man/woman	Age (years) (Mean $\pm$ SD) (T/C)	T	C	Main outcomes
Mitsuboshi <i>et al.</i> ¹⁷	10	9/1	61.5 $\pm$ 12.2	Topiroxostat	Placebo	Uric acid
Hosoya <i>et al.</i> ¹⁸	62/60	109/13	62.5 $\pm$ 8.8/ 64.6 $\pm$ 8.1	Topiroxostat	Placebo	Blood pressure, urine protein positive rate and adverse reactions
Matsuo <i>et al.</i> ¹⁹	46/48	66/28	61.8 $\pm$ 12.8/ 61.9 $\pm$ 12.5	Topiroxostat	Placebo	Uric acid and eGFR
Katsuyama <i>et al.</i> ²⁰	41	27/14	64.4 $\pm$ 11.8	Topiroxostat	Placebo	Uric acid, eGFR and urine protein positive rate
Mizukoshi <i>et al.</i> ²¹	40/40	62/18	69.8 $\pm$ 9.4/ 68.6 $\pm$ 12.0	Topiroxostat	Placebo	Blood pressure
Nagaoka <i>et al.</i> ²²	27	21/6	62 $\pm$ 10/ 62 $\pm$ 16	Topiroxostat	Placebo	Uric acid
Wada <i>et al.</i> ²³	43/22	57/8	60.5 $\pm$ 10.1/ 63.0 $\pm$ 8.7	Topiroxostat	Placebo	Adverse reactions

T: Trial group and C: Control group

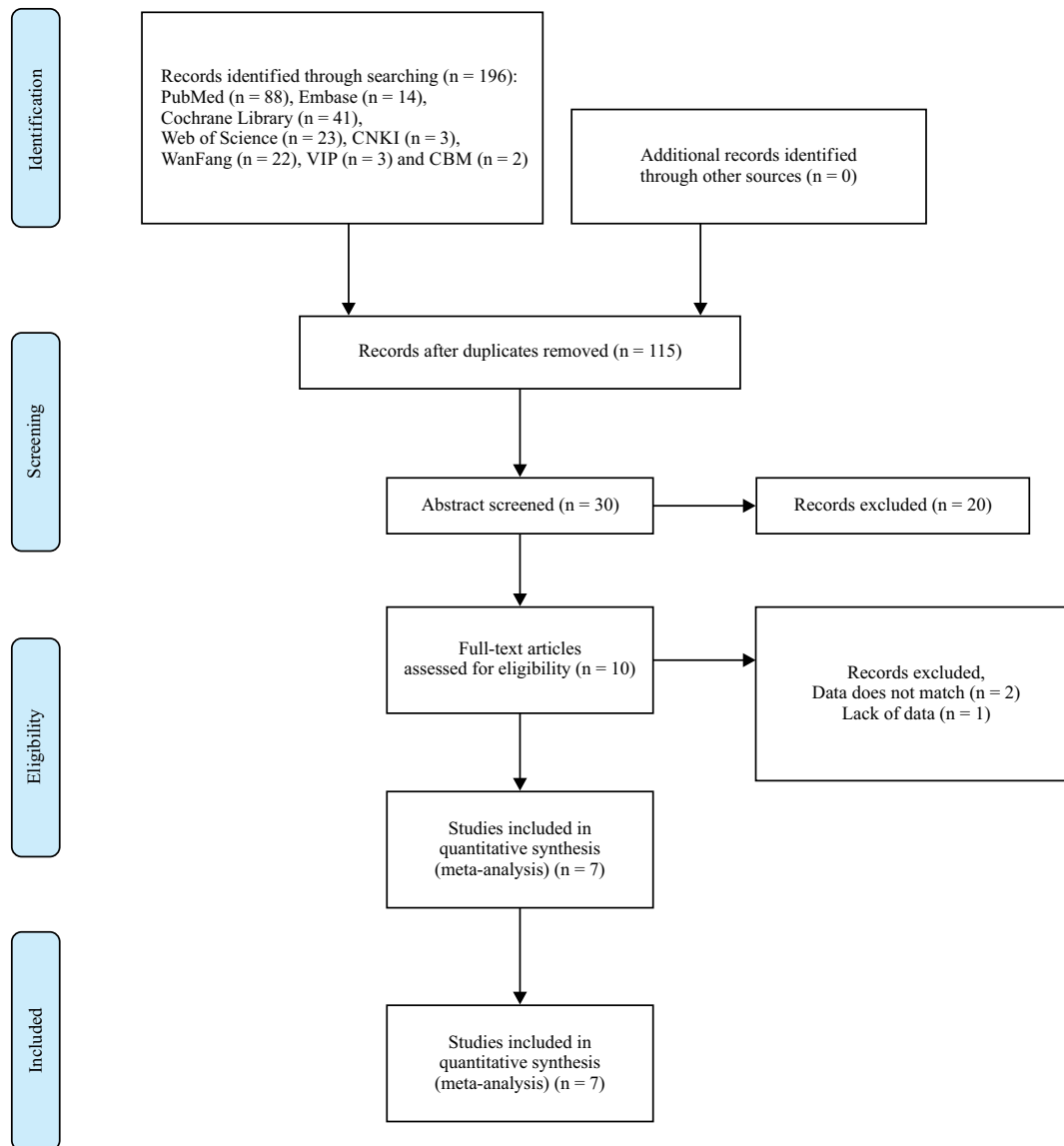


Fig. 1: Expresses the flowchart of screening for inclusion in the literature of meta-analyses (PRISMA)

Diastolic blood pressure: Two studies reported the diastolic BP of the study category and the control population. According to meta-analysis, the experimental group's diastolic blood pressure did not change substantially from the control group (Fig. 9; SMD: -0.76; 95% CI: -4.42, 2.91; $p = 0.685$). All of these studies' results had low variability and a sensitivity analysis was done (Fig. 10).

Urine protein positive rate: The prevalence of urine protein positivity in the sample population and two inquiries were reported on the control group. The results of a meta-analysis revealed that the experimental group's urine protein positive

rate did not differ substantially from the control group (SMD: 0.55; 95% CI: 0.25, 1.22; $p = 0.143$, Fig. 11). All of these studies' results had low variability and a sensitivity analysis was done (Fig. 12).

Adverse reactions: Two investigations provided evidence of the detrimental impacts on the test and control groups. According to the findings of a meta-analysis, there was no tangible variation between unfavorable responses of the experimental group and those of the control condition (SMD: 1.16; 95% CI: 0.78, 1.72; $p = 0.459$, Fig. 13). All of these studies' results had low variability and a sensitivity analysis was done (Fig. 14).

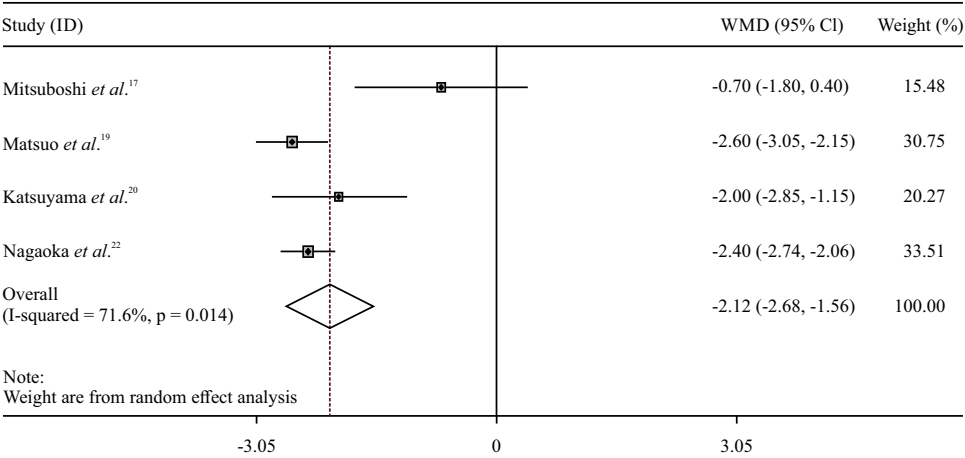


Fig. 2: Forest illustration of the uric acid

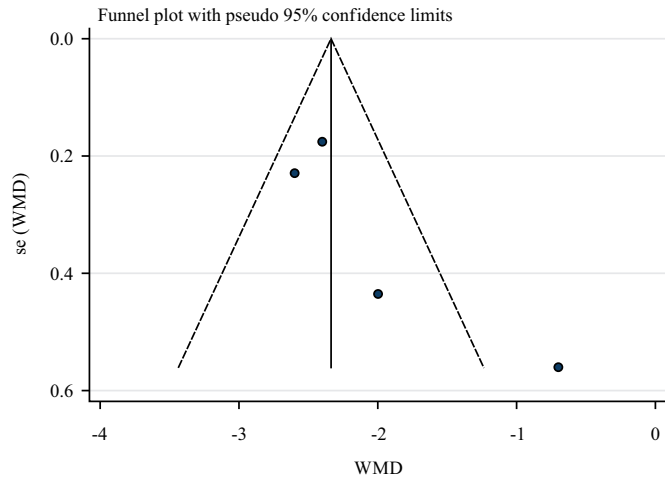


Fig. 3: Funnel plot of the uric acid

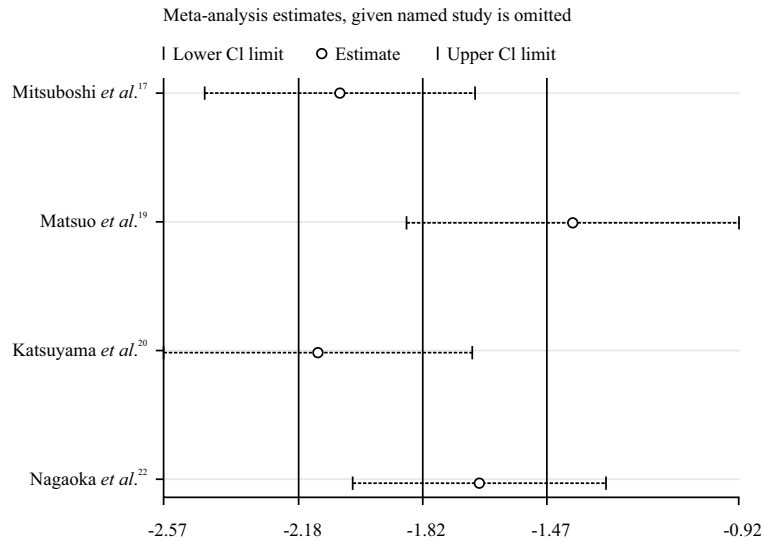


Fig. 4: Sensitivity analysis of the uric acid

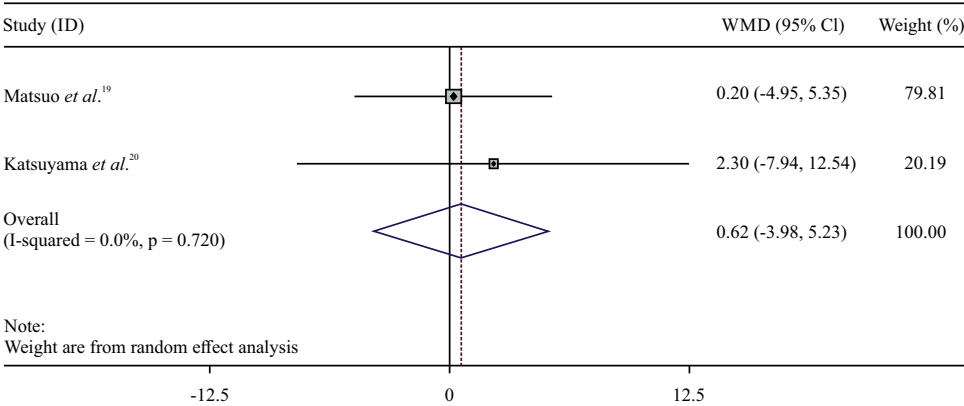


Fig. 5: Forest illustration of the eGFR

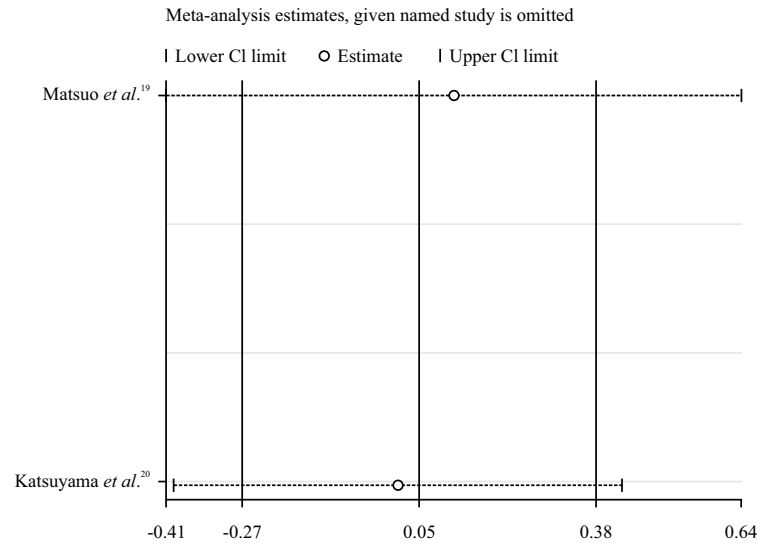


Fig. 6: Sensitivity analysis of the eGFR

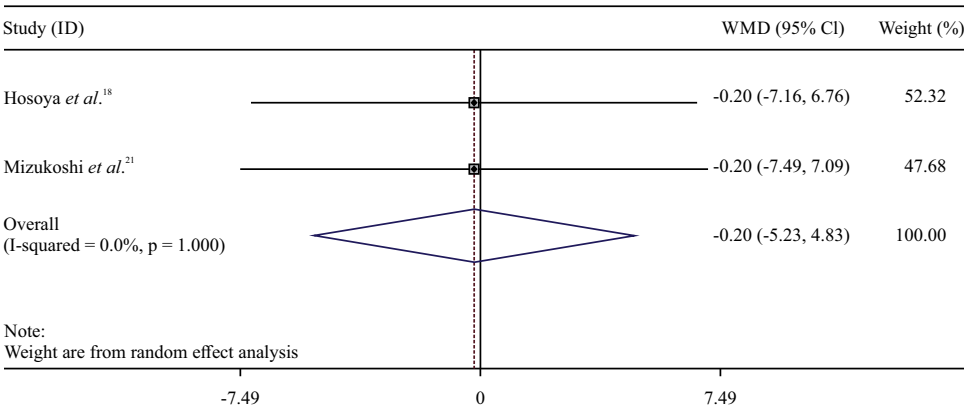


Fig. 7: Forest illustration of the systolic blood pressure

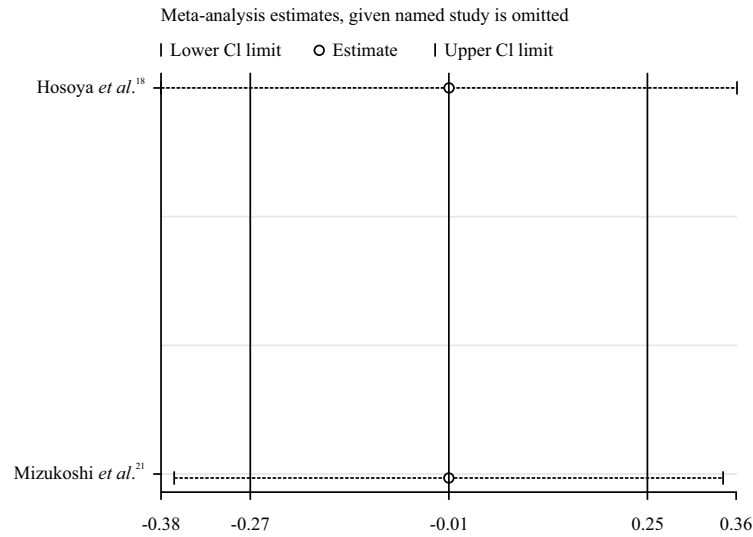


Fig. 8: Sensitivity analysis of the systolic blood pressure

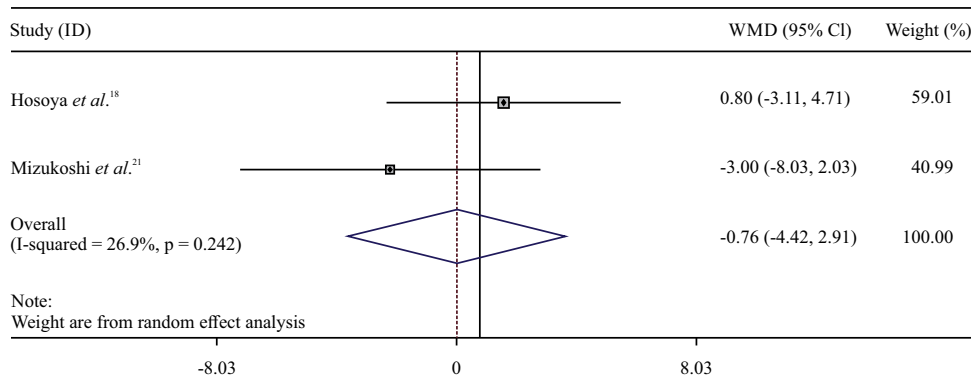


Fig. 9: Forest illustration of the diastolic blood pressure

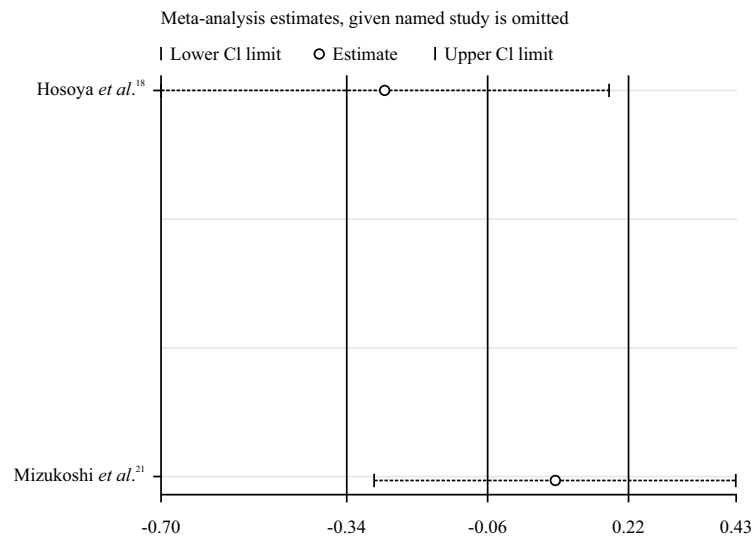


Fig. 10: Sensitivity analysis of the diastolic blood pressure

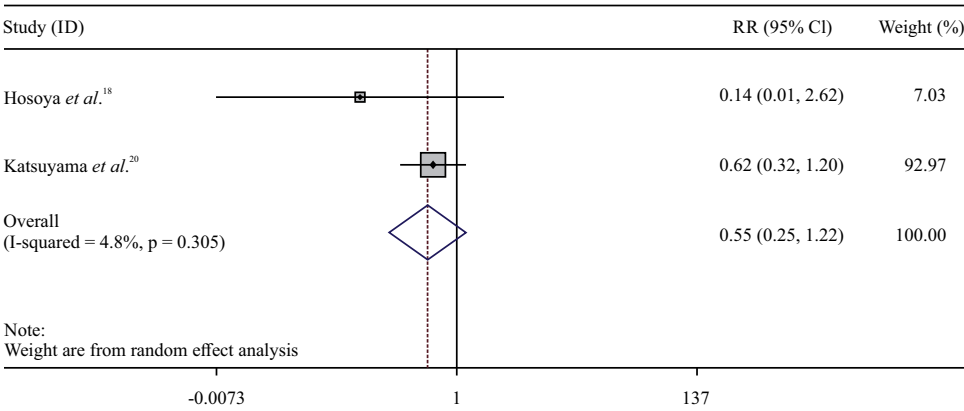


Fig. 11: Forest illustration of the urine protein positive rate

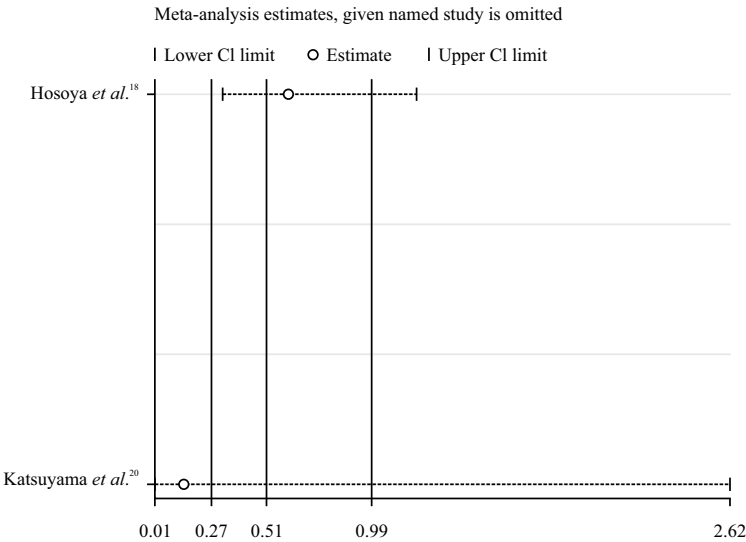


Fig. 12: Sensitivity analysis of the urine protein positive rate

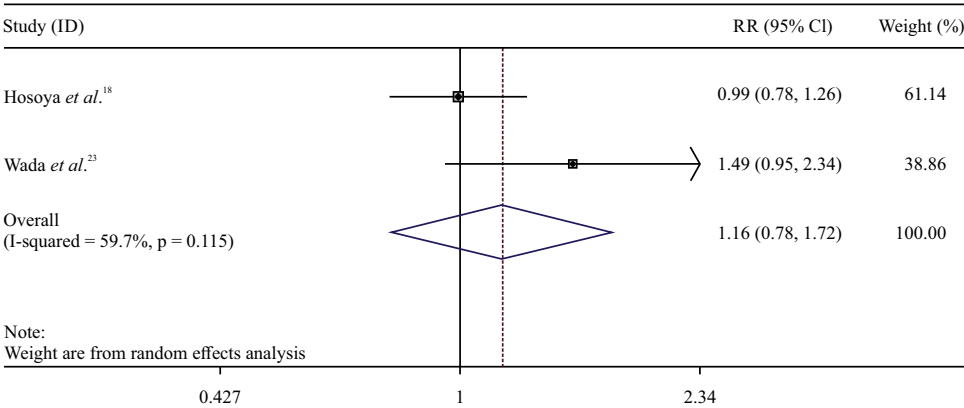


Fig. 13: Forest illustration of the adverse reactions

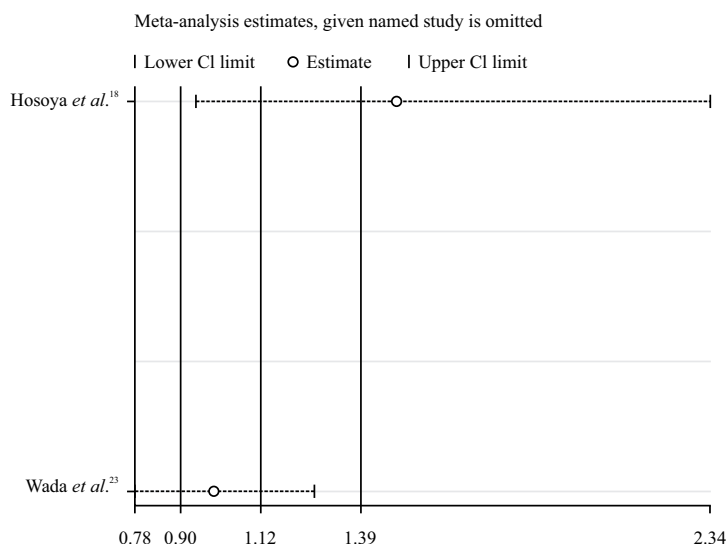


Fig. 14: Sensitivity analysis of the adverse reactions

DISCUSSION

This study investigated 7 literary works¹⁷⁻²³ including 269 individuals in the experimental category and 248 in the comparison group. Study participants' topiroxostat for HUA and chronic renal illness had decreased uric acid values than comparison subjects, per a meta-analysis. The meta-analysis revealed acceptable uric acid levels in the experimental class (SMD: -2.12; 95% CI: -2.68, -1.56; $p < 0.01$). As per the findings of the eGFR meta-analysis, the test group eGFR was not considerably distinct from that of the control group when compared to the latter (SMD: 0.62; 95% CI: -3.98, 5.23; $p = 0.790$). According to a meta-analysis of systolic BP, the test group systolic BP did not significantly vary from that of the control population when compared to them (SMD: -0.20; 95% CI: -5.23, 4.83; $p = 0.938$). The meta-analysis of diastolic BP revealed that the diastolic BP of the test cohort was not significantly distinct from that of the control cohort when compared with the control cohort (SMD: -0.76; 95% CI: -4.42, 2.91; $p = 0.685$). There was no discernible difference among the urine protein positive rates of the test group and the control group, according to the results of the meta-analysis of the urine protein positive incidence (SMD: 0.55; 95% CI: 0.25, 1.22; $p = 0.143$). The findings of the meta-analysis of adverse reactions showed that there was no statistically meaningful difference between the adverse reactions in the test group as well as the control group when compared to the control group (SMD: 1.16; 95% CI: 0.78, 1.72; $p = 0.459$).

In recent years, epidemiological data from around the world show that the annual prevalence of chronic kidney illness is rising and the global kidney health problem is facing great challenges²⁴. Previously, the primary risk factors for the

decline of kidney function were proteinuria, hypertension, diabetes and other conditions. However, now, metabolic factors like serum uric acid and lifestyle-related factors gradually harm and contribute to the development of chronic kidney failure²⁵. Renal injury can be caused directly by the formation of uric acid crystals in the kidneys. Additionally, increased serum uric acid can result in glomerular hypertension, glomerulosclerosis, interstitial fibrosis, systemic hypertension and other conditions via the number of pathways unrelated to crystal formation, including activation of RAS, stimulate T cells and macrophages, activate MCP-1, NF- κ B and TNF- α , activate NADPH oxidase, damage mitochondria and change the phenotype of renal tubular cells and other mechanisms²⁶. The main mechanism of high uric acid-induced renal injury may be endothelial cell dysfunction through increased oxidative stress and decreased NO bioavailability. Recent studies have found that amino acid metabolism disorders and unbalanced gut flora are significant contributors to the development of HUA-induced kidney failure²⁷. As per epidemiological studies, HUA accurately forecasts the start of persistent kidney disease in individuals who have normal renal function, like in the general population and in individuals who have diabetes²⁸. Bravo *et al.*²⁹ performed a retrospective analysis of 291 living kidney donors. By showing that serum uric acid was an independent indicator of chronic renal failure [eGFR 60 mL/min/(1.73 m²)] in female donors 1 year after kidney donation, a logit regression analysis supported the likelihood of HUA. It has been found that gender plays a deleterious role in persistent kidney disease and that it may have an effect on the likelihood that someone will develop renal failure.

The search was limited to Chinese and English literature; no literature in any other language was found; there may have been insufficient study inclusion and there could have been bias in selection. Consequently, you should be impartial when evaluating some of these meta-finding analyses.

CONCLUSION

According to the study's findings, topiroxostat may be helpful for people with chronic renal disease and high uric acid levels, as evidenced by uric acid. However, topiroxostat did not significantly improve the levels of eGFR, urine protein positive rate or blood pressure. More high-quality research is required to confirm the aforementioned findings.

SIGNIFICANCE STATEMENT

The rate of hyperuricemia (HUA) and chronic renal disease has been rapidly rising in recent years, with significant implications for public health. This meta-analysis examines the efficacy of topiroxostat in patients with chronic renal disease and hyperuricemia, comparing it to another group of patients also receiving topiroxostat. The study's results suggest that topiroxostat may be beneficial for those with chronic renal illness and elevated levels of uric acid, as shown by uric acid levels. Nevertheless, topiroxostat did not provide a substantial improvement in the levels of eGFR, urine protein positive rate, blood pressure or any other factors.

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