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Research Article

A Meta-Analysis for Comparing the Effects of Febuxostat and Allopurinol on Kidney Function in Hyperuricemia Patients Complicated with Chronic Kidney Disease

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Background. This study was designed to assess the effects of febuxostat on the uric acid level and kidney function of hyperuricemia (HUA) patients complicated with chronic kidney disease (CKD). *Methods*. A computer-based search was conducted on the China National Knowledge Infrastructure (CNKI), Wanfang, PubMed, and Web of Science databases from the inception of the databases to April 2023 to identify clinical randomized controlled trials on HUA and CKD, with comparisons between febuxostat and allopurinol as variables of interest. The meta-analysis was conducted using Stata v17.0. *Results*. Eighteen studies were included in this meta-analysis, encompassing a total of 1877 patients. These patients were segregated into a control group (treated with allopurinol or placebo) consisting of 1039 individuals and an experimental group (treated with febuxostat alone or a combination of febuxostat with other therapies) comprising 838 patients. The meta-analysis revealed that patients in the experimental group, treated with febuxostat, exhibited a significantly higher estimated glomerular filtration rate (eGFR) than those in the control group treated with allopurinol (weighted mean difference (WMD): 2.897, 95% CI: 1.336 to 4.458, $P < 0.001$). In addition, the experimental group demonstrated significantly lower levels of serum creatinine (WMD: −17.810, 95% CI: −24.147 to −11.474, $P < 0.001$), serum uric acid (WMD: −91.891, 95% CI: −117.609 to −66.173, $P < 0.001$), and blood urea nitrogen (WMD: −1.284, 95% CI: −1.837 to −0.731, $P < 0.001$). However, there was no significant difference in 24-hour urinary protein quantity (WMD: −0.198, 95% CI: −0.413 to 0.016, $P = 0.070$) between the two groups. *Conclusion*. These findings suggest that febuxostat may offer a more beneficial therapeutic option for managing CKD in hyperuricemic patients. However, the observed heterogeneity and the limited diversity of the study population warrant cautious interpretation of these results.

1. Introduction

Hyperuricemia (HUA) is a common medical condition characterized by a substantial increase in fasting serum uric acid (SUA) levels, exceeding 420 μmol/L while maintaining a standard purine-rich diet. Uric acid, a product of purine metabolism, is primarily excreted through the renal and intestinal pathways. HUA is defined by SUA levels greater than 7.0 mg/dl in males and 5.7 mg/dl in females [1]. Presently, HUA has emerged as a significant public health issue. In the years 2015-2016, the prevalence of gout in the United States reached 3.9% among adults, with rates of 5.2% in men and 2.7% in women [2]. Epidemiological data from 2015 to 2018 in China highlight the substantial burden of HUA, with an overall prevalence rate of 19.87%, encompassing rates of 28.35% in males and 9.41% in females [3].

In recent years, the mounting incidence of HUA has led to a growing understanding of its detrimental effects on the human body. A substantial body of research has elucidated the correlation between HUA and the onset and progression of various medical conditions, including kidney disease, gout, cardiovascular and cerebrovascular diseases, and metabolic syndrome [4]. Among these, HUA demonstrates a significant and direct association with chronic kidney disease (CKD) and related kidney conditions, including end-stage kidney disease, albuminuria, and elevated serum creatinine (SCr) levels [5]. Elevated SUA levels in the body can instigate kidney injury by precipitating sodium urate

crystal deposition in the tubular interstitium, triggering oxidative stress reactions, and activating the renin-angiotensin system through increased renin expression in periglomerular cells [6]. Therefore, actively managing SUA levels stands as a crucial strategy for slowing the progression of CKD, with measures primarily including lifestyle interventions and pharmaceutical treatments.

Allopurinol, a traditional medicine widely used, is effective in suppressing uric acid synthesis. Goicoechea et al. [7] reported that allopurinol can mitigate kidney injury resulting from HUA, leading to reductions in urinary protein, blood urea nitrogen (BUN), and SCr levels to some extent while also ameliorating pathological kidney tissue changes. Nonetheless, allopurinol, being a purine analog, can also affect the activity of other enzymes involved in purine metabolism and is associated with numerous adverse reactions; thus, it is not recommended in the treatment of elderly patients with moderate to severe kidney dysfunction [8]. Febuxostat, on the other hand, is a nonpurine selective inhibitor of xanthine oxidase that robustly inhibits uric acid synthesis. It is excreted via both bile and the kidneys and is accompanied by fewer adverse reactions [9]. Although some studies have confirmed that febuxostat can more effectively lower uric acid levels than allopurinol (in doses of 300/200 mg), there remains a lack of research and evidence regarding the efficacy and safety of febuxostat in the treatment of HUA patients with moderate to severe kidney dysfunction [10].

In this study, we hypothesized that treatment with febuxostat could be more effective than allopurinol in managing patients with CKD complicated by HUA. Thus, we designed this present study by conducting a meta-analysis to compare the effects of febuxostat and allopurinol and evaluate their efficacies and safety on HUA patients complicated with CKD.

2. Materials and Methods

2.1. Search Strategies. This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. Data were retrieved from the Wanfang, China National Knowledge Infrastructure (CNKI), PubMed, and Web of Science databases. The following are effective terms and related variants used in the database searches: "Hyperuricemia," "Chronic kidney disease," "Febuxostat," and "Allopurinol." These keywords and their corresponding MeSH terms were combined with the Boolean operators AND or OR. The complete keyword search terms were used for PubMed were (Chronic kidney disease [Title/Abstract] OR Kidney Insufficiency, Chronic [Title/Abstract] OR Chronic Renal Insufficiency [Title/Abstract] OR Renal Insufficiency, Chronic [Mesh]) AND (Hyperuricemia [Mesh]) AND (Allopurinol [Mesh]) AND (Febuxostat [Title/Abstract] OR Uloric [Mesh]). Chinese databases use the appropriate search terms in Chinese. The search timeframe included records from the inception of each database up to April 2023.

2.2. Inclusion and Exclusion Criteria. The inclusion criteria comprised (1) randomized controlled trials (RCTs) as the only research design, necessitating the documentation of participants' general details, including name, age, and gender, along with the recording of biochemical indicators such as BUN, SCr, SUA, and microalbumin levels; (2) patients clinically diagnosed with CKD complicated by HUA; and (3) SUA levels exceeding 420 μmol/L for males and 360 μmol/L for females, as well as an estimated glomerular filtration rate (eGFR) lower than ml/min/1.73 m^2. Intervention in the experimental group involved either febuxostat alone or a combination of febuxostat with other therapeutic modalities, while the control group received treatment with allopurinol or a placebo. The outcome measures included eGFR, SCr, 24-hour urinary protein quantity (24-h UTP), SUA, and BUN levels, with at least one of these measures required for inclusion in each study.

The exclusion criteria included the following: (1) studies involving letters, reviews, animal studies, case reports, secondary analyses, and any non-RCT; (2) studies involving patients undergoing dialysis, kidney transplantation, individuals with malignant tumors, kidney failure, or those aged below 18 years; (3) lacked kidney function-related outcomes; and (4) did not provide original data or presented incomplete research data required for our present study analysis.

2.3. Literature Screening and Data Extraction. After removing duplicate literature, two researchers independently screened the title, abstract, and full text of the potentially eligible articles. Disagreements were resolved by involving a third researcher. Data extraction was performed that included authorship, publication date, language, study duration, study population, intervention methods, sample size, and experimental endpoints. Subsequently, data from the selected literature were compared to assess the efficacy and safety of febuxostat and allopurinol in treating CKD complicated by HUA. Efficacy was evaluated based on eGFR, SCr, 24-h UTP, SUA, and BUN. Safety was assessed by monitoring adverse events and complications. Last, the Cochrane risk-of-bias tool was used to evaluate literature quality.

2.4. Statistical Analysis. All data were analyzed using Stata 17.0 (StataCorp LLC, College Station, TX, USA). Continuous variable results are shown as the weighted mean difference (WMD) and 95% confidence interval (CI). A significance level of $P < 0.05$ was used to denote statistical significance, and all tests were two-tailed. Heterogeneity among the included studies was evaluated using the Q test and I^2 statistic. If I^2 exceeded 50% and $P < 0.10$, indicating notable heterogeneity, we used the random-effects model for data synthesis; otherwise, the fixed-effects model was utilized. Sensitivity analysis was performed to identify potential sources of heterogeneity and assess the stability of the meta-analysis results.

3. Results

3.1. Search Outcomes. Based on the search strategies, a total of 472 studies were initially identified, with 56 retrieved from PubMed, 263 from Web of Science, 27 from Wanfang, and 126 from CNKI. Following the removal of duplicated studies, 127 were excluded based on search records, and an additional 279 were excluded based on abstracts and titles. Subsequently, the full text of 30 articles was evaluated, among which 12 records were excluded due to one instance of missing data, seven studies with mismatched research design types, and four studies being non-RCT. Thus, a total of 18 studies were included in this meta-analysis [12–29]. The detailed literature search process is shown in Figure 1, and Figures 2(a) and 2(b) present the risk of bias graph and the risk of bias summary, respectively.

The basic characteristics of the eligible articles are shown in Table 1. Collectively, this meta-analysis comprised 18 RCTs, encompassing a total of 1,877 patients, with 1,039 individuals in the control group and 838 in the experimental group. Among the 18 RCTs, two were identified from non-Chinese databases, while the remaining 16 were from Chinese databases. The publication dates of these trials ranged from 2019 to 2022, with experimental durations ranging from 12 months to 36 months, and all trials were conducted within China. The mean age of the patients across the studies ranged from 30.4 to 84.4 years, the ratio varied from approximately 1 : 2 to 4 : 5, and the treatment duration extended from 4 to 24 weeks.

3.2. Outcomes of Meta-Analysis

3.2.1. Primary Outcome Measures. Eleven reports [12–14, 18, 19, 22–25, 28, 29] provided data on the eGFR levels in both patient groups posttreatment and exhibited significant heterogeneity ($I^2 = 80.1\%$; $P < 0.1$), requiring the use of the random-effects model for meta-analysis. The analysis results demonstrated that the eGFR levels in the experimental group were significantly higher than those in the control group (WMD: 2.897, 95% CI: 1.336 to 4.458, $P < 0.001$) (Figure 3(a)). Sensitivity analysis indicated that the exclusion of any individual study did not alter the overall combined analysis results (Figure 3(b)). Moreover, the outcomes of Begg's test ($P = 0.640$) and Egger's test ($P = 0.323$) indicated the absence of publication bias in the eGFR results.

3.2.2. Secondary Outcome Measures. The comparison of SCr levels in HUA patients with CKD after treatment with febuxostat and allopurinol was based on data from 10 studies [12, 13, 17, 19–25]. Four studies [17, 18, 24, 25] provided information on changes in UTP in both treatment groups posttreatment. In addition, 14 articles [14–25, 27, 29] reported on SUA levels between the two groups after treatment, while 7 papers [19, 20, 22, 23, 25, 26, 29] presented data on BUN levels. In all these studies, significant heterogeneity was observed ($I^2 > 50\%$; $P < 0.1$), warranting the application of the random-effects model for data synthesis. Meta-analysis results (Figures 4(a)–4(d)) indicated significantly lower levels of SCr (WMD: −17.810, 95% CI: −24.147 to −11.474, $P < 0.001$), SUA (WMD: −91.891, 95% CI: −117.609 to −66.173, $P < 0.001$), and BUN (WMD: −1.284, 95% CI: −1.837 to −0.731, $P < 0.001$) in the experimental group than those in the control group. However, the level of UTP (WMD: −0.198, 95% CI: −0.413 to 0.016, $P = 0.070$) did not exhibit a significant difference.

The sensitivity analysis results (Figures 5(a)–5(d)) demonstrated that the exclusion of any individual study, one by one, did not exert any notable impact on the overall outcomes of this analysis, confirming the reliability and validity of the meta-analysis results. Furthermore, the results of both Begg's test and Egger's test indicated the absence of publication bias in the outcomes of SCr (Begg's test: $P = 0.592$; Egger's test: $P = 0.367$), UTP (Begg's test: $P = 0.734$; Egger's test: $P = 0.849$), SUA (Begg's test: $P = 0.228$; Egger's test: $P = 0.326$), and BUN (Begg's test: $P = 1.000$; Egger's test: $P = 0.478$).

4. Discussion

Allopurinol is the primary therapeutic agent for HUA to reduce uric acid production by inhibiting hypoxanthine and xanthine metabolism. Nevertheless, the overall clinical efficacy of allopurinol remains suboptimal. Notably, uric acid levels often do not exhibit significant reductions in most patients, and complications from allopurinol are not uncommon [14]. We designed this present study based on the rationale of the known association between HUA and CKD and the potential benefits of urate-lowering therapies such as febuxostat and allopurinol in managing HUA. Our results reveal that febuxostat treatment was associated with a significant improvement in eGFR compared to allopurinol, indicating a potential benefit for kidney function. Furthermore, febuxostat led to significant reductions in SCr, SUA, and BUN levels, suggesting its effectiveness in managing HUA and preserving renal function. These findings may be particularly relevant for clinicians managing such patients with HUA, offering a more effective pharmacological intervention. However, considering that there was no statistically significant difference in the 24-h UTP between the two treatment groups, this highlights the need for further research to confirm these observations and assess long-term safety.

The findings that febuxostat treatment was associated with a significant improvement in eGFR compared to allopurinol in HUA patients with CKD may be attributed to several potential underlying mechanisms. First, HUA is known to trigger inflammatory responses in the kidneys [30], potentially leading to renal damage, and febuxostat has been suggested to have anti-inflammatory properties that could help reduce inflammation in the renal tissues [31]. Febuxostat's capacity to inhibit the overexpression of insulin-like growth factor and basic fibroblast growth factor in the kidney may have also suppressed the formation of granulomas induced by monocyte proliferation in the local area, thereby delaying or mitigating further deterioration of kidney function and preserving normal renal filtration

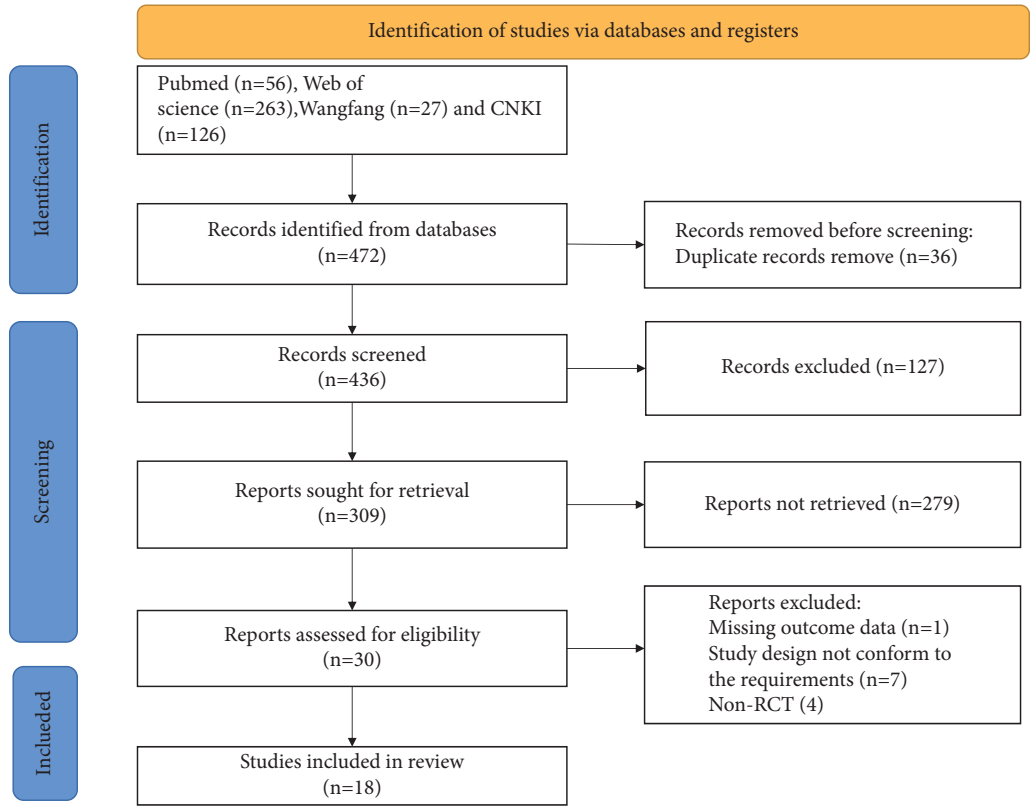
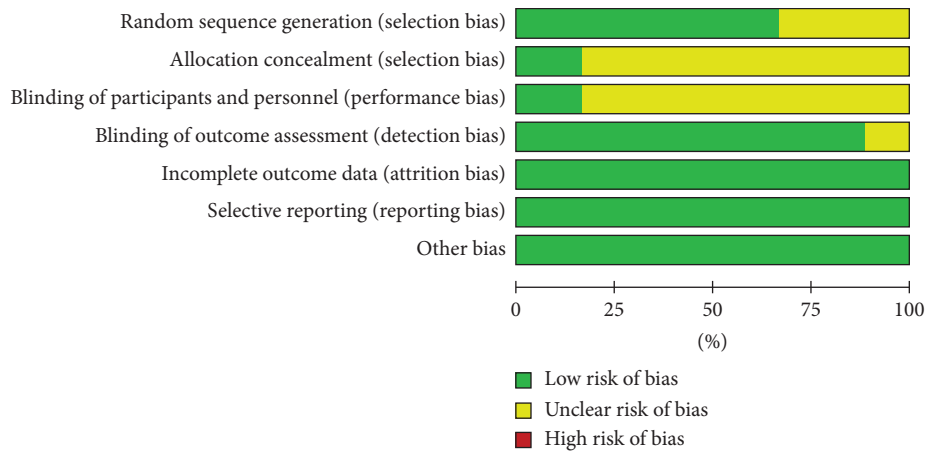


Figure 1: Literature search process.



(a)

Figure 2: Continued.

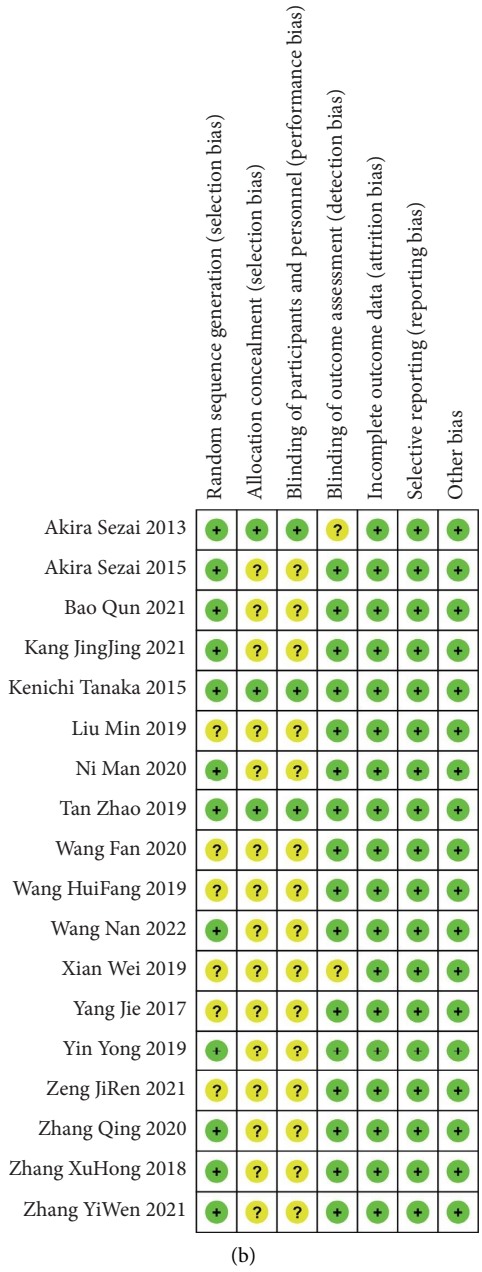


Figure 2: Risk of bias graph for the included literature. (a) Risk of bias graph; seven areas were scored for risk of bias; (b) Risk of bias summary; each item of bias was scored as low (+), uncertain (?), or high risk (−).

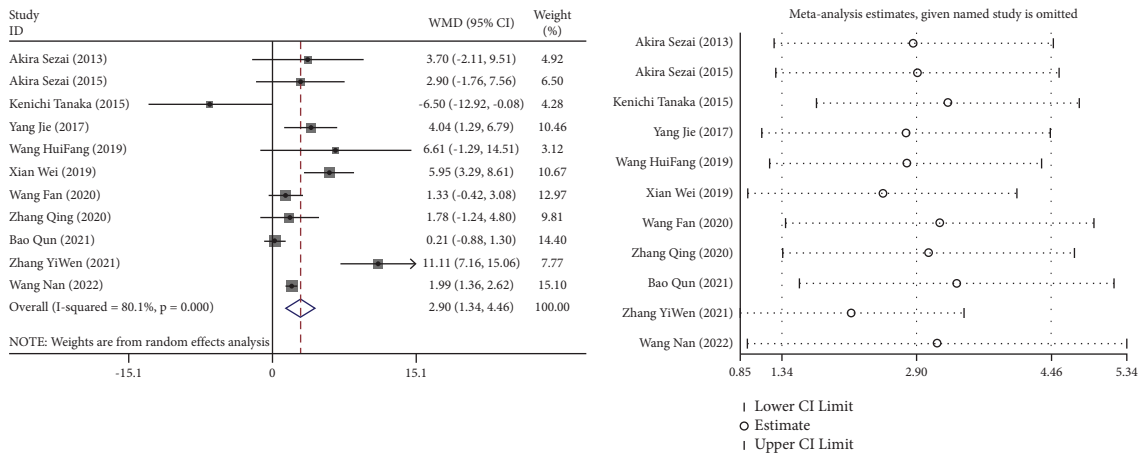
capabilities [32]. Second, some studies have suggested that febuxostat may improve endothelial function [33], which plays a role in regulating blood flow to the kidneys. Improved endothelial function could result in better renal perfusion and function. Third, HUA can lead to increased oxidative stress, which can damage renal cells, and febuxostat's ability to lower SUA levels may have reduced oxidative stress in the kidneys, protecting them from injury [34]. Fourth, febuxostat and allopurinol have distinct mechanisms of action. Febuxostat is a selective xanthine oxidase inhibitor, whereas allopurinol is a nonselective xanthine oxidase inhibitor [35]. The selectivity of febuxostat may make it more effective at lowering uric acid levels, which could have a positive impact on kidney function. Last, in some cases, the combination of febuxostat with other therapeutic modalities in the experimental group may have contributed to the observed improvement in eGFR. These additional interventions could include blood pressure management, anti-inflammatory agents, or other treatments that benefit kidney functions.

Furthermore, compared with the control group, HUA patients complicated with CKD who received febuxostat exhibited a significant reduction in SUA levels. Xanthine oxidase plays a crucial role in catalyzing the conversion of hypoxanthine into xanthine and subsequently into uric acid. Allopurinol, functioning as a xanthine oxidase inhibitor,

Table 1: The basic characteristics of inclusion in the literature.

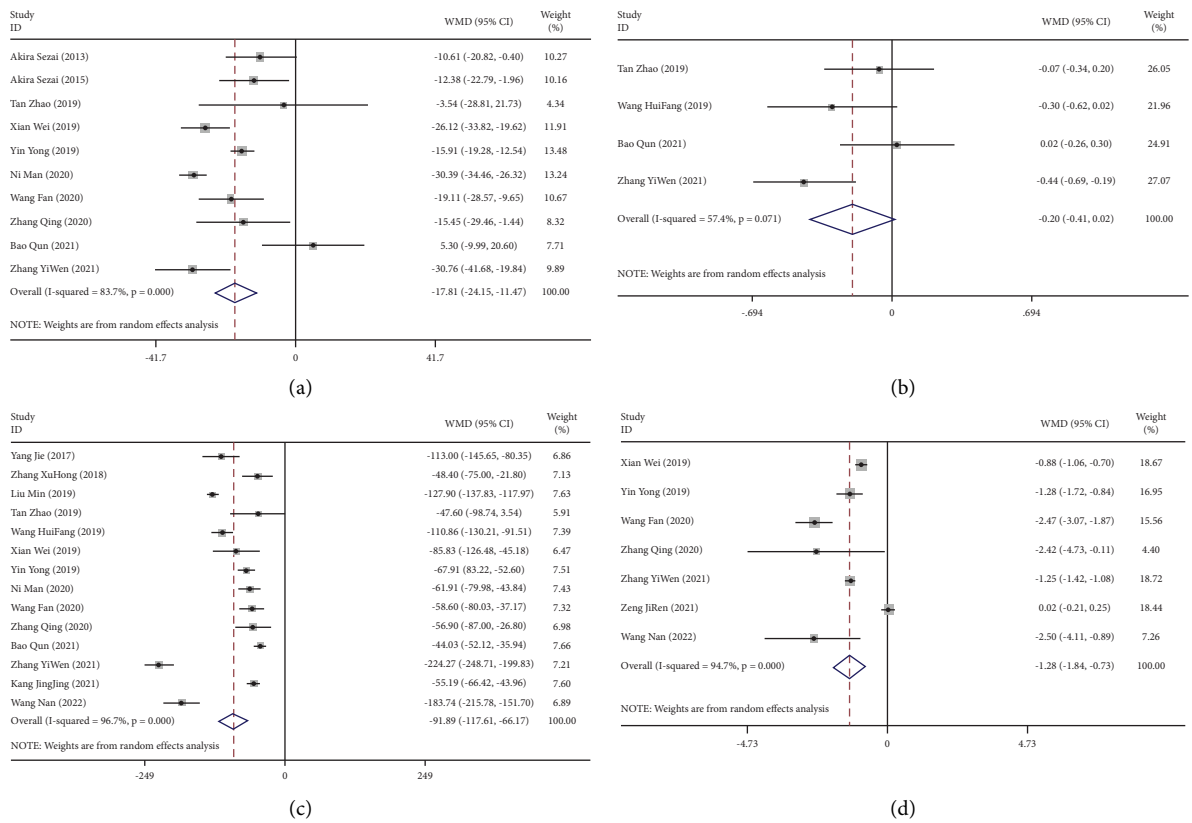
No	Study	Year	Nation	Duration	Patients	Intervention		Number (F/M)		Age		Course of treatment	Random	Outcomes
						Experimental group	Control group	Experimental group	Control group	Experimental group	Control group			
1	Akira Sezai	2013	Japan	—	CKD4 complicated with HUA	Febuxostat	Allopurinol	13/58	12/57	67.4 ± 9.7	66.4 ± 10.8	6 mon	RCT	①②
2	Akira Sezai	2015	Japan	—	CKD3 complicated with HUA	Febuxostat	Allopurinol	13/43	11/42	69.4 ± 10.0	69.1 ± 9.2	6 mon	RCT	①②
3	Kenichi Tanaka	2015	Japan	2012.04–2013.03	CKD3 complicated with HUA	Febuxostat	Allopurinol	2/19	3/16	70.1 ± 9.5	66.1 ± 7.0	3 mon	RCT	②
4	Yang Jie	2017	China	2015.11–2016.05	CKD3-4 complicated with HUA	Febuxostat	Allopurinol	10/20	12/18	42.5 ± 12.1	44.1 ± 11.5	2 mon	RCT	②④
5	Zhang XuHong	2018	China	2014.08–2016.02	CKD1-3 complicated with HUA	Febuxostat	Allopurinol	11/23	7/27	76.5 ± 7.9	74.8 ± 8.9	6 mon	RCT	④
6	Liu Min	2019	China	2016.12–2017.08	CKD1-3 complicated with HUA	Febuxostat	Allopurinol	13/33	12/34	66.2 ± 5.3	67.5 ± 4.9	6 mon	RCT	④
7	Tan Zhao	2019	China	2015.02–2016.12	CKD3 complicated with HUA	Febuxostat	Allopurinol	7/32	9/30	54.2 ± 9.7	55.8 ± 10.1	6 mon	RCT	①③④
8	Wang HuiFang	2019	China	2015.06–2016.06	CKD3-5 complicated with HUA	Febuxostat	Allopurinol	14/37	17/30	51.39 ± 15.04	52.72 ± 15.12	6 mon	RCT	②③④
9	Xian Wei	2019	China	2015.10–2017.10	CKD1-3 complicated with HUA	Febuxostat	Allopurinol	23/31	25/29	66.4 ± 7.3	67.2 ± 7.5	6 mon	RCT	①②④⑤
10	Yin Yong	2019	China	2016.01–2017.09	CKD4-5 complicated with HUA	Febuxostat	Allopurinol	14/29	13/30	47.38 ± 6.50	47.58 ± 6.60	2 mon	RCT	①④⑤
11	Ni Man	2020	China	2018.08–2019.08	CKD complicated with HUA	Febuxostat	Allopurinol	22/31	20/33	61.09 ± 4.87	61.32 ± 5.19	6 mon	RCT	①④
12	Wang Fan	2020	China	2016.08–2019.08	CKD1-3 complicated with HUA	Febuxostat	Allopurinol	10/40	11/39	70.7 ± 6.2	70.4 ± 6.1	6 mon	RCT	①②④⑤
13	Zhang Qing	2020	China	2017.01–2019.05	CKD2-4 complicated with HUA	Febuxostat	Allopurinol	12/18	14/16	56.00 ± 12.00	51.00 ± 15.00	6 mon	RCT	①②④⑤
14	Bao Qun	2021	China	2019.01–2019.12	CKD3-5 complicated with HUA	Febuxostat	Allopurinol	20/32	17/33	58.65 ± 0.47	58.86 ± 0.51	6 mon	RCT	①②③④
15	Zhang YiWen	2021	China	2016.08–2019.01	CKD4-5 complicated with HUA	Febuxostat	Allopurinol	35/32	33/34	55.1 ± 9.4	54.2 ± 8.4	6 mon	RCT	①②③④⑤
16	Zeng JiRen	2021	China	2020.06–2020.12	CKD complicated with HUA	Febuxostat	Allopurinol	19/21	18/22	—	—	6 mon	RCT	⑤
17	Kang JingJing	2021	China	2018.02–2020.06	CKD2-4 complicated with HUA	Febuxostat	Allopurinol	20/25	18/27	64.21 ± 2.14	64.16 ± 2.12	6 mon	RCT	④
18	Wang Nan	2022	China	2020.03–2021.01	CKD4-5 complicated with HUA	Febuxostat	Allopurinol	208/49	22/47	81.35 ± 2.52	81.40 ± 2.49	1 mon	RCT	②④⑤

RCT: randomized controlled trial; F/M: female/male; CKD: chronic kidney disease; HUA: hyperuricemia; ① SCr, serum creatinine; ② eGFR, estimated glomerular filtration rate; ③ 24-h UPQ, 24-hour urinary protein quantity; ④ SUA, serum uric acid; ⑤ BUN, blood urea nitrogen.



(a) (b)

Figure 3: Meta-analysis of eGFR of HUA patients complicated with CKD after treatment with febuxostat and allopurinol. (a, b) The eGFR of HUA patients complicated with CKD after treatment was assessed by a forest plot (a) and a sensitivity analysis diagram (b). eGFR, estimated glomerular filtration rate; HUA, hyperuricemia; CKD, chronic kidney disease.



(a) (b)

(c) (d)

Figure 4: Meta-analysis of kidney function indexes of HUA patients complicated with CKD after treatment with febuxostat and allopurinol. (a–d) Forest plots for assessing the levels of SCr (a), 24-h UTP (b), SUA (c), and BUN (d) in HUA patients complicated with CKD. SCr, serum creatinine; 24-h UTP, 24-hour urinary protein quantity; SUA, serum uric acid; BUN, blood urea nitrogen; HUA, hyperuricemia.

diminishes uric acid production by suppressing xanthine oxidase activity [36]. In contrast, febuxostat selectively targets uric acid synthesis without significantly impacting the activities of other enzymes related to pyrimidine or purine metabolism. Furthermore, febuxostat can interact with sodium bicarbonate, facilitating the dissolution and excretion of urate, resulting in a substantial reduction in SUA levels among CKD patients complicated with HUA [37]. In addition, febuxostat has been shown to reduce or ameliorate pathological changes in afferent arterioles,

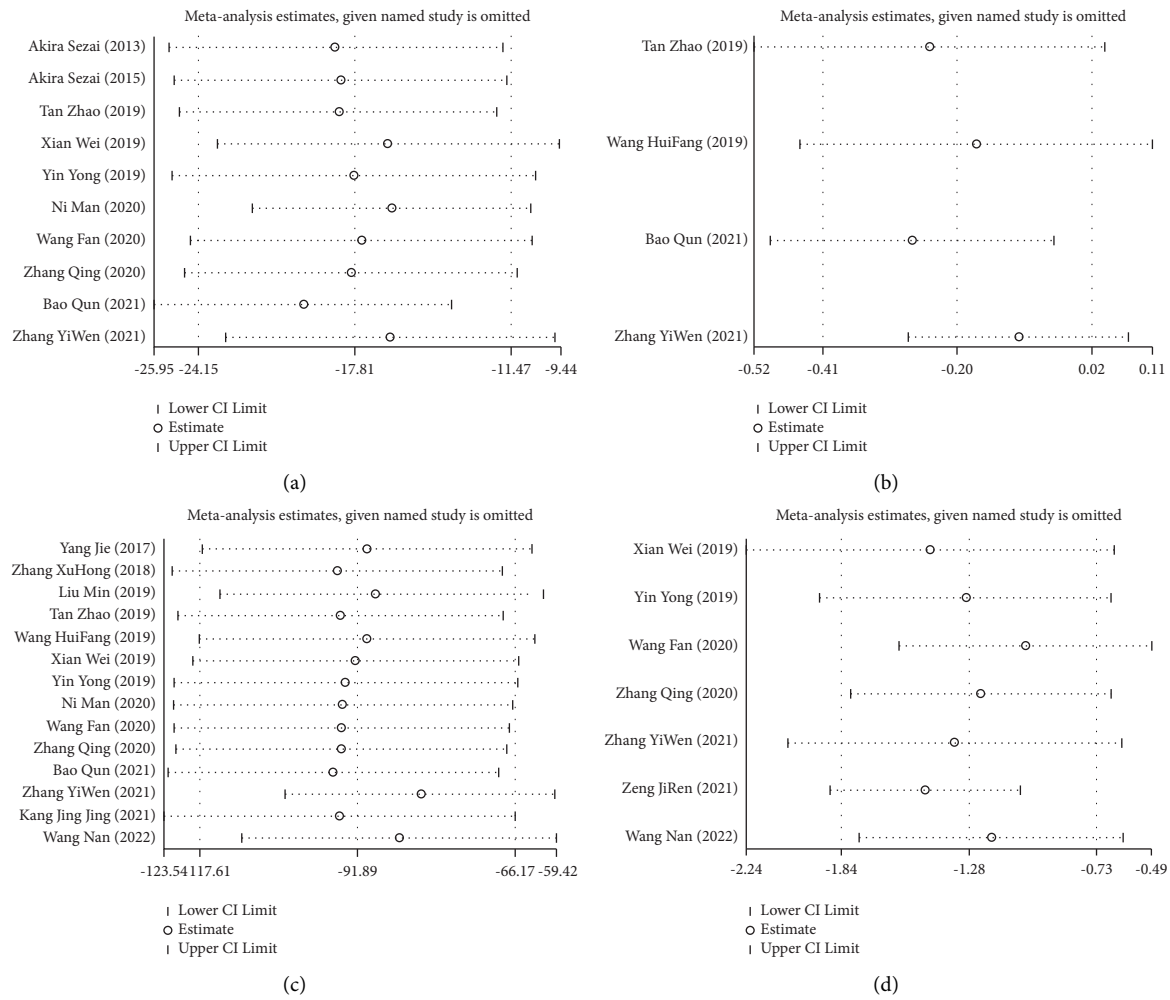


Figure 5: Sensitivity analysis for the kidney function indexes of HUA patients complicated with CKD after treatment with febuxostat and allopurinol. (a–d) Sensitivity analysis for levels of SCr (a), 24-h UTP (b), SUA (c), and BUN (d). SCr, serum creatinine; 24-h UTP, 24-hour urinary protein quantity; SUA, serum uric acid; BUN, blood urea nitrogen; HUA, hyperuricemia; CKD, chronic kidney disease.

glomerular hypertrophy, sclerosis, proteinuria induced by high uric acid levels, and mild tubulointerstitial fibrosis [38]. The Japanese Society of Gout and Nucleic Acid Metabolism (JSGNM) and the Dutch College of General Practitioners (DCGP) recommend lowering SUA levels below 6 mg/dL using uric acid-lowering drugs to protect kidney function in HUA patients [39, 40].

Quantitative measurement of urinary protein plays a vital role in the diagnosis, treatment, and outcomes of patients with CKD, with the 24-h UTP test serving as the gold standard for total urinary protein determination [41]. However, the analysis did not reveal a significant difference in 24-h UTP levels between the experimental and control groups (WMD: −0.198, 95% CI: −0.413 to 0.016, $P = 0.070$). This lack of a significant difference between the two groups may be attributed to several potential factors. First, the relatively short treatment durations in the included studies (ranging from 4 to 24 weeks) might not have allowed sufficient time to observe significant changes in proteinuria, which often develops and progresses over a longer timeframe. For instance, in a recent study by O'Dell et al., patients with gout and HUA were randomly assigned allopurinol or febuxostat in a 72-week trial. The trial had three phases (titration (weeks 0 to 24), maintenance (weeks 25 to 48), and observation (weeks 49 to 72). O'Dell et al. found that allopurinol was noninferior to febuxostat in controlling flares and similar outcomes were noted in participants with stage 3 CKD [42]. However, it should be noted that although 300 mg is the most commonly prescribed dose of allopurinol, in the study of O'Dell et al., the authors used a titrate-to-target protocol, and the median dose of allopurinol to achieve the target was 400 mg, while 29% of participants needed 500 mg or higher. Second, the heterogeneity in patient populations, comorbidities, and treatment regimens across the included studies may have contributed to variations in proteinuria outcomes.

Moreover, our present meta-analysis results demonstrated that the experimental group exhibited notably lower SCr levels, showed a more pronounced advantage in reducing SCr, and displayed significantly lower BUN levels than the control group. SCr and BUN are widely used clinical indices for assessing kidney function, and

simultaneous elevation of both indicators indicates severe kidney impairment [43]. Conversely, the concurrent reduction of SCr and BUN can effectively alleviate kidney damage. These findings indicate that febuxostat can improve eGFR, lower SUA levels, and enhance SCr and BUN-related parameters. Moreover, febuxostat holds substantial pharmaceutical values, which aligns closely with the findings of another meta-analysis by Zheng and Sun [44], which indicated that febuxostat may be effective in patients with CKD and HUA. Importantly, our investigations into drug safety revealed the absence of severe adverse reactions in both treatment groups, highlighting the safety and reliability of both therapeutic approaches. However, it should be noted that the CAREs trial reported that febuxostat increased cardiovascular and all-cause mortality compared with allopurinol [45], which led the U.S. FDA to issue a boxed warning in 2019, while the FAST trial [46] and that of O'Dell et al. [42] showed no indication that febuxostat increases the risk of major adverse cardiovascular events or is associated with greater cardiovascular mortality or overall mortality. Furthermore, it should also be noted that allopurinol was studied in two trials of HUA in participants with heart failure, with conflicting results [47, 48].

While the meta-analysis conducted in this study provides valuable insights into the efficacy and safety of febuxostat and allopurinol in treating HUA patients complicated by CKD, there are several limitations to consider when interpreting the results of this meta-analysis. First, the inclusion of studies conducted exclusively from China and predominantly in the Chinese population may limit the generalizability of the findings to more diverse populations. Second, the heterogeneity observed in various outcome measures, such as eGFR, SCr, 24-hour urinary protein quantity, SUA, and BUN levels, despite the use of random-effects models, suggests potential variations in study designs, patient characteristics, or interventions across the included trials. Third, the relatively short duration of some of the trials may not capture long-term outcomes or potential adverse effects that may emerge over extended treatment periods. In addition, we did not perform a subgroup analysis for elderly individuals, who often are more likely to have multiple comorbidities and be on various medications, which could have potentially affected treatment outcomes and interactions. Thus, further research and meta-analysis, encompassing diverse populations and longer follow-up periods, are essential to validate these results and assess the safety profile of febuxostat in patients with HUA and CKD.

5. Conclusion

Our findings demonstrate that febuxostat treatment was associated with significant improvements in key clinical parameters, including increased eGFR and reduced levels of SCr, SUA, and BUN, when compared to allopurinol. Overall, these results suggest that febuxostat may represent a more promising therapeutic approach for this specific patient population. However, it is important to acknowledge the limitations of this study and the need for further research, encompassing diverse populations and longer follow-up periods, to validate these results and assess the safety profile of febuxostat in patients with HUA and CKD.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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