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The effect of initiation of urate-lowering treatment during a gout flare on the current episode: a meta-analysis of randomized controlled trials

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Abstract

Objective: The objective was to evaluate whether initiation of urate-lowering treatment (ULT) during an acute gout flare prolonged the current episode.

Methods: A comprehensive search of MEDLINE and Web of Science databases was conducted from their inception to 15 March 2021. Five randomized controlled trials (RCTs) with 381 patients met the inclusion criteria. Standardized mean difference (SMD), odds ratio (OR), and 95% confidence interval (CI) were used for estimating the clinical efficacy of ULT in acute gout.

Results: There was no statistical difference in days to resolution (intent-to-treat analysis) (SMD, 0.68; 95% CI − 0.42 to 1.78; I^2, 49%; $p=0.22$), the pain visual analogue score (VAS) by day 10 (SMD, − 0.07; 95% CI − 0.30 to 0.16; I^2, 0%; $p=0.53$), C-reactive protein (CRP) from day 7 to 10 (SMD, − 1.14; 95% CI − 5.63 to 3.36; I^2, 55%; $p=0.62$), erythrocyte sedimentation rate (ESR) from day 7 to 10 (SMD, − 2.51; 95% CI − 5.46 to 0.45; I^2, 0%; $p=0.10$) and the recurrence of gout flares within 28–30 days (OR 0.78; 95% CI 0.29 to 2.09; I^2, 0%; $p=0.62$).

Conclusion: Initiation of ULT during an acute gout flare did not prolong the duration of the flare. However, larger sample size studies are needed to confirm this finding.

Trial registration number PROSPERO (CRD42021234581).

Keywords: Gout, Meta-analysis, Urate-lowering therapy

Introduction

Gout is a common arthritic condition that results from monosodium urate (MSU) crystal deposition. Previous guidelines have provided conflicting recommendations on whether urate-lowering treatment (ULT) could be initiated during an acute gout flare [1–3]. Generally, ULT should be initiated after an acute flare has resolved to avoid prolongation of the current episode [4]. The incidence of gout flares has been positively correlated with the reduction of serum uric acid (sUA) levels in the first 3–6 months after initiating ULT [5].

However, ULT could be initiated during an acute flare to reduce the number of outpatient visits, and increase patient compliance [6–8]. The 2016 EULAR Gout Management Recommendations did not provide any clear

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guidance on ULT [9] due to prolong the current episode. The accepted cause may be that ULT leads to MSU redistribution and induces inflammation. The 2020 American College of Rheumatology (ACR) guidelines for the management of gout have conditionally recommended that pharmacological ULT could be initiated during an acute gout flare [3]. However, the recommendation was graded moderate based on two small randomized controlled trials (RCTs) [10, 11]. The two RCTs observed that initiating allopurinol treatment during an acute gout flare did not prolong the days to resolution [11]. Febuxostat (40 mg/day) had a superior urate-lowering effect compared to limited allopurinol doses (maximum 200–300 mg/day) [5, 12]. At present, two RCTs have been published on the initiation of febuxostat for acute gout flares [13, 14].

A systematic literature review identified the effect of initiation of allopurinol or azapropazone during an acute gout flare [15]. However, it did not include any RCT on febuxostat. Hence, the present study aimed to systematically review the literature to identify whether initiation of ULT during an acute gout flare prolongs the current episode.

Methods

Literature search

A literature search according to the Population, Intervention, Comparator and Outcomes (PICO) framework was performed and the criteria for study eligibility were established. We performed a systematic review of articles published in MEDLINE (via PubMed), Cochrane library, EMBASE and Web of Science databases from their inception to March 2021. Keywords included 'acute gout', 'allopurinol', 'febuxostat', 'Benzbromarone', 'azapropazone', 'urate-lowering treatment', 'clinical trial'. The search was limited to articles published in English, and RCTs in patients older than 18 years. We chose studies evaluating the inflammation after initiation of ULT vs. placebo during an acute gout attack. We first screened abstracts, and then chose relevant full-text articles. The reference lists of selected articles were manually searched to identify additional relevant reports.

Study selection

The types of studies considered for inclusion were randomized, placebo-controlled trials comparing the inflammation after initiation of ULT with placebo in patients with an acute gout attack. The exclusion criteria were as follows: (i) trials comparing different doses of the same medication only, (ii) studies without a designated intervention/comparator arm, (iii) the presence of inflammatory diseases other than gout, and (iv) studies reported in a language other than English.

Data extraction

Two investigators independently extracted the relevant information using a predefined data collection form. For each trial, patient characteristics, treatment modalities, control group characteristics, follow-up duration, evaluation criteria and main findings were collected. Disagreements were resolved by consensus between the two investigators. We attempted to contact the authors for missing data.

Endpoints

The primary endpoint was the time to remission of gout flare. Secondary endpoints were as follows: Pain on visual analogue score (VAS), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), recurrent gout flares and dropouts.

Risk of bias

The two reviewers independently assessed the risk of bias of the included studies by means of the risk of bias (ROB) tool. This instrument consists of 7 aspects: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Any differences will be analyzed by the third reviewer. Any inconsistencies are resolved by discussion with the third reviewer.

Certainty of the evidence

The quality of evidence across pooled studies (risk of bias, inconsistency, indirectness, and imprecision) was assessed by two researchers (EJ and XY) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach with the online version of GRADEproGDT software (www.gradepro.org, McMaster University, 2016). Summary-of-findings tables were created for every rated outcome based on Cochrane-compliant rules. Disagreements were resolved by discussion between the two researchers or by consulting a third author (HG) for arbitration.

Statistical analysis

The odds ratios (ORs) of non-progressors was estimated for each study by comparing ULT vs. placebo. The ORs were then pooled using the DerSimonian and Laird method if heterogeneity was present; otherwise they were pooled using a fixed-effect model. For continuous outcomes, mean difference of days to resolution between ULT and placebo was estimated for each study and then pooled across studies using standardized mean difference (SMD). Heterogeneity

was assessed using Q statistics and the degree of heterogeneity was quantified using I^2. If heterogeneity was detected ($p \leq 0.05$ or $I^2 \geq 50\%$), a random-effect model was applied; otherwise, a fixed-effect model was used. All statistical analyses were performed using RevMan 5.3 (The Cochrane Collaboration, United Kingdom).

Sensitivity analysis was performed to assess the stability of the model and carried out by using different statistical models (fixed-effect model vs. random-effect model). Sensitivity analysis was restricted to primary outcomes.

Results

Characteristics of included studies

A detailed flowchart of the results of the literature search is shown in Fig. 1. We identified 184 studies in MEDLINE and Web of Science databases from their inception to 15 March 2021, and two additional studies were manually added. Of these 186 studies, five studies met the inclusion criteria and were included [10, 11, 13, 14, 16]. Among the five retrieved RCTs between 1987 and 2021, two RCTs used allopurinol [10, 11], two RCTs used febuxostat [13, 14], and one RCT used azapropazone [16]. A total of 381 patients were included in our analysis. The quality of the studies is shown in Table 1. Risk of bias is shown in Additional file 1: Fig. S1.

Days to resolution

The outcome of the days to resolution was reported in two studies [11, 14], which included 161 patients, with 79 patients in the experimental group and 82 patients in the control group. Intent-to-treat analysis and per protocol analysis were used for Mate analysis of these two RCTs. There was no significant difference in days to resolution (intent-to-treat analysis) between the experimental group and the control group (SMD, 0.68; 95% CI − 0.42 to 1.78; I^2, 49%; $p = 0.22$) (Fig. 2). Similarly, there was no significant difference in the days to resolution (per protocol analysis) between the two groups (SMD, 0.49; 95% CI − 0.67 to 1.65; I^2, 0%; $p = 0.41$) (Additional file 2: Fig. S2).

Pain on visual analogue score (VAS) by day 10

Three studies reported the VAS on day 10 [10, 11, 13]. Hill et al. did not provide specific data and we could not get in touch with the author before submitting the manuscript. A meta-analysis was conducted on the other two studies, which included 59 patients in the experimental group and 50 patients in the control group. There was no significant difference in VAS by day 10 between the two groups (SMD, − 0.07; 95% CI − 0.30 to 0.16; I^2, 0%; $p = 0.53$) (Fig. 3).

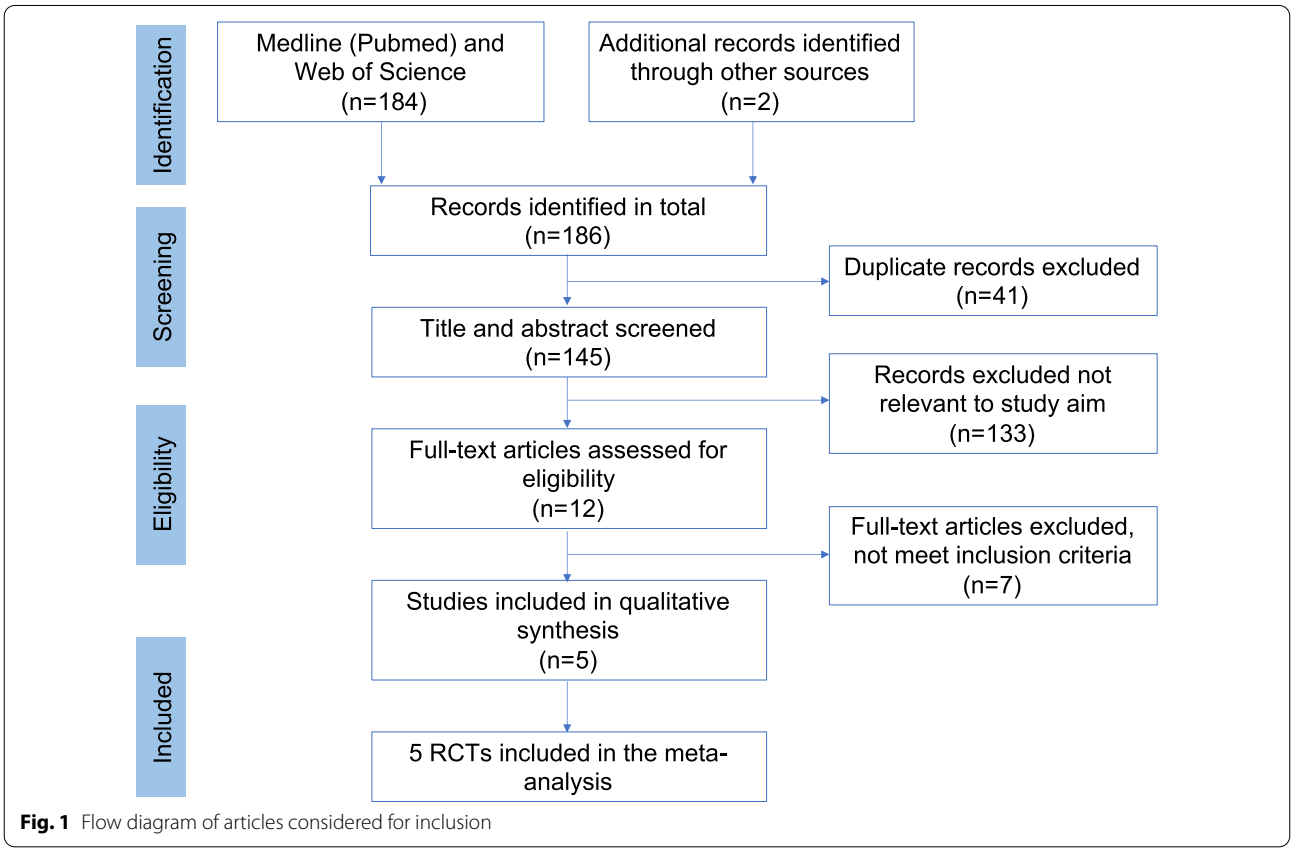

Fig. 1 Flow diagram of articles considered for inclusion

Table 1 Characteristics of patients and intervention in included studies

Study	Blinding	No. of patient (% of male)	Age, years	Follow-up time	Background therapy	Study arms	Jadad score	Certainty of the evidence (GRADE)	Outcomes	*p* value
Jia E 2021	Single-blind	E: 70 (97.14) C: 70 (97.14)	E: 42.13 C: 41.41	28 days	Diclofenac 75 mg BID (1–7 days), Diclofenac 75 mg QD (8–28 days) for the remission period	E: Febuxostat 40 mg QD (1–28 days), C: Placebo (1–7 days) + Febuxostat 40 mg QD (1–28 days)	4/5	M	1. Duration of acute gout 2. Joint pain (1, 3, 5, 7 days) 3. Joint swelling (1, 3, 5, 7 days) 4. Joint tenderness (1, 3, 5, 7 days) 5. Joint erythema (1, 3, 5, 7 days) 6. The rate of resolution within 7 days 7. CRP (7 days) 8.ESR (7 days) 9.SUA (7 days) 10.gout flares (8–28 days)	1. = 0.578 2. > 0.05 3. > 0.05 4. > 0.05 5. > 0.05 6. = 0.284 7. = 0.513 8. = 0.610 9. = 0.000 10. = 0.492
Hill Erica M 2015	Double-blind	E: 16 (87.5) C: 19 (100)	E: 60.63 C: 53.11	28 days	Colchicine or NSAIDs	E: allopurinol 100 mg QD (1–14 days), allopurinol 200 mg QD (15–28 days) C: Placebo (1–28 days)	5/5	M	1.SUA 2.VAS 3. Gout flares 4. Duration of acute gout	1. = 0.012 2. N/R 3. N/R 4. = 0.13
Taylor Thomas H 2012	Double-blind	E: 31 (100) C: 26 (100)	E: 58 C: 62	30 days	Indomethacin 50 mg TID (1–10 days) + colchicine 0.6 mg BID (1–90 days)	E: allopurinol 300 mg QD (1–30 days) C: Placebo (1–10 days) + allopurinol 300 mg QD (11–30 days)	5/5	M	1. VAS 2. ESR (1, 3, 10, 30 days) 3. hs-CRP (1, 3, 10, 30 days) 4. SUA (1 days) 5. SUA (3 days, 10 days) 6. SUA (30 days) 7.gout flares (1–30 days)	1. = 0.62 2. > 0.05 3. > 0.05 4. = 0.759 5. < 0.001 6. = 0.423 7. = 0.61

Table 1 (continued)

Study	Blinding	No. of patient (% of male)	Age, years	Follow-up time	Background therapy	Study arms	Jadad score	Certainty of the evidence (GRADE)	Outcomes	*p* value
Sun Ruixia 2020	NR	E: 30 (—) C: 26 (—)	E: 41 C: 44.50	12 weeks	Etoricoxib for one week (120 mg per day for 3 days and then 60 mg per day for 4 days)	E: Febuxostat 40 mg QD (1–28 days), C: Placebo (1–14 days) + Febuxostat 40 mg QD (1–28 days)	3/5	L	1. Gout flares (12 weeks) 2.VAS (1–14 days) 3. CRP (1, 3, 7, 14 days) 4. ESR (1, 3, 7, 14 days) 5. Interleukin-1β (1, 3, 7, 14 days) 6. tumor necrosis factor-α (1, 3, 7, 14 days) 7. SUA (3, 7, 14 days)	1. = 0.45 2. > 0.05 3. > 0.05 4. > 0.05 5. > 0.05 6. > 0.05 7. < 0.05
Fraser R. C 1987	Double-blind	E: 47 (—) C: 46 (—)	–	225 days	–	E: azapropazone 600 mg tid (1–4 day), azapropazone 600 mg BID (5–225 day) C: —	5/5	M	1. Gout flares (1–8 months) 2. SUA (4 days, 1–8 months)	1. = NR 2. < 0.05 (4 days and 28 days), > 0.05 (2–8 months)

E experiment group, C control group, NSAIDs nonsteroidal anti-inflammatory drugs, VAS pain visual analogue score, SUA serum uric acid, QD once a day, BID twice a day, TID three times a day, CRP C-reactive protein, ESR erythrocyte sedimentation rate;

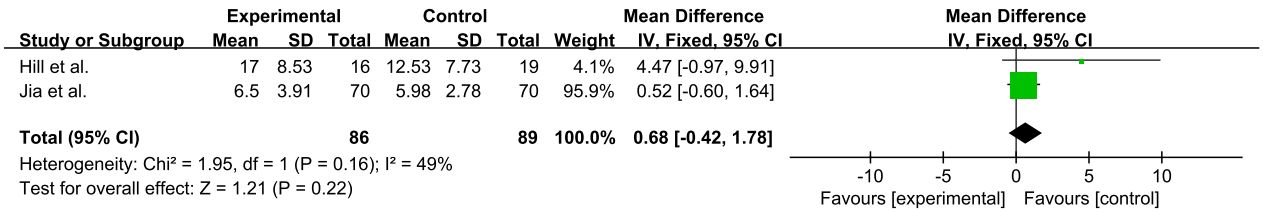

Fig. 2 Forest plot of the days to resolution (intent-to-treat analysis) between the experimental group and the control group

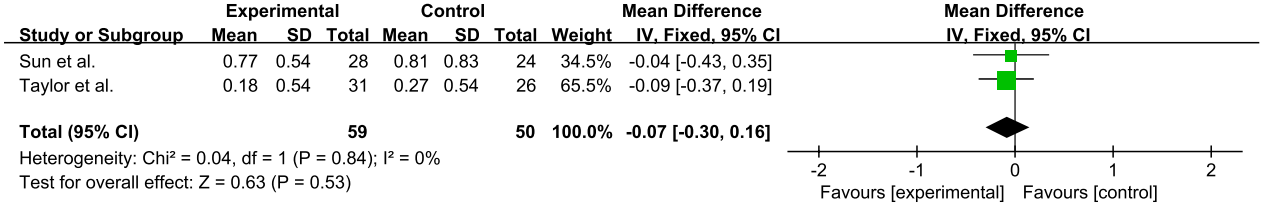

Fig. 3 Forest plot of the VAS by day 10 between the experimental group and the control group

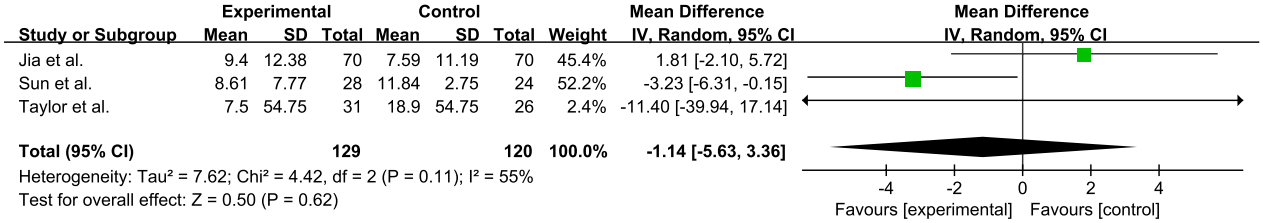

Fig. 4 Forest plot of the CRP by day 7–10 between the experimental group and the control group

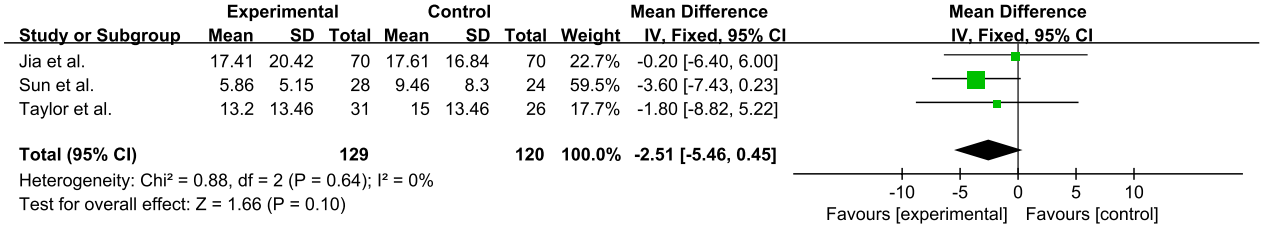

Fig. 5 Forest plot of the ESR by day 7–10 between the experimental group and the control group

CRP and ESR by day 7 to 10

A total of 249 patients were included in three studies [10, 13, 14], with 129 patients in the experimental group and 120 patients in the control group. There was no significant difference in CRP levels between the two groups from day 7 to day 10 (SMD, − 1.14; 95% CI − 5.63 to 3.36; I^2, 55%; $p = 0.62$) (Fig. 4).

A total of 249 patients were included in three studies [10, 13, 14], with 129 patients in the experimental group and 120 patients in the control group. There was no significant difference in ESR level between the two groups from day 7 to 10 (SMD, − 2.51; 95% CI − 5.46 to 0.45; I^2, 0%; $p = 0.10$) (Fig. 5).

Recurrent gout flares within 30 days

Three studies [10, 13, 14] reported the gout flares within day 28 to 30, including 101 patients in the experimental group and 102 patients in the control group. There was no significant difference in the number of gout flares between the two groups within day 28 to 30 (OR 0.78;

95% CI 0.29 to 2.09; I^2, 0%; $p=0.62$) (Additional file 3: Fig. S3).

Dropouts and sensitivity analysis

A total of 381 patients were reported in all studies [10, 11, 13, 14, 16], including 194 patients in the experimental group and 187 patients in the control group. There was no significant difference in the number of dropouts between the two groups (OR 1.10; 95% CI 0.62 to 1.96; I^2, 0%; $p=0.74$) (Additional file 4: Fig. S4). We performed a sensitivity analysis of the days to resolution (Intent-to-treat analysis) by random-effects meta-analysis instead of a fixed-effect approach. Thus, the result was consistent with it in the fixed-effect model (MD, 1.56; 95% CI − 1.85 to 4.98; $p=0.37$) (Additional file 5: Fig. S5).

Discussion

A previous systematic literature review identified the effect of initiation of allopurinol or azapropazone during an acute gout flare [15], however, it did not include any RCT on febuxostat. Another systematic literature review identified the effect of initiation of allopurinol and febuxostat [17], however, the quality of the studies was low. Hence, this updated review was conducted with higher quality of studies than the previous review [17].

The main reason why some doctors advise against ULT in acute gout flares is that it may prolong the duration of inflammation. The outcome of the days to resolution was reported in two studies [11, 14]. In one of the trials, allopurinol was initiated at 100 mg daily for the first 14 days and then increased to 200 mg daily for the next 14 days [11]. The investigators observed that the days to resolution were 15.4 days for the allopurinol group and 13.4 days for the placebo group ($p=0.05$). Ertao Jia [14] found that the mean days to resolution was 5.98 days for the placebo group and 6.50 days for the febuxostat group ($p=0.578$). This review showed no significant difference in days to resolution. VAS results showed that the pain degree was similar between the ULT and placebo groups. There was no significant difference in CRP and ESR between the two groups from day 7 to day 10. Hence, initiation of ULT for acute gout flare did not prolong the current episode.

Recurrent gout flares were another concern for gout patients after initiation of ULT. The incidence of gout flare was 12–61% in the first six months [5, 18]. This review found no significant difference in the incidence of gout flares between the two groups within 28–30 days. Hence, initiation of ULT should be based on adequate anti-inflammation [3]. Non-steroidal anti-inflammatory drugs were administered in the studies, and their side effects were digestive tract discomfort, elevated transaminase and decreased GFR.

This review had some limitations. The included sample size was small (381 subjects), which may affect the accuracy and extrapolation of the results. The variations among the subjects and medication plans (drug variety, dosage, duration of treatment) may have led to clinical heterogeneity in the results. Since this review only included five RCTs, subgroup analysis was not performed. Although this review strictly followed the strategy to search publicly published literatures, some published literatures, conference literatures and gray literatures may be missing, leading to publication bias.

Conclusions

This study showed that initiation of ULT during an acute gout flare did not prolong the duration of acute flares. However, larger sample size studies are needed to confirm this finding.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42358-022-00236-5.

Additional file 1: Fig. S1. Risk of bias.

Additional file 2: Fig. S2. Forest plot of the days to resolution (per protocol analysis) between the experimental group and the control group.

Additional file 3: Fig. S3. Forest plot of the recurrent gout flares within 28–30 days between the experimental group and the control group.

Additional file 4: Fig. S4. Forest plot of the dropouts between the experimental group and the control group.

Additional file 5: Fig. S5. Forest plot of the sensitivity analyses.

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Authors' contributions

EJ, JZ and XY designed the study. EJ, HG and XY drafted the manuscript. LZ, JX, YX, YJ, XQ, MX, YZ, DT and JW reviewed the research. EJ, XY and HG were responsible for the statistical analyses. All authors read and approved the final manuscript.

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Availability of data and materials

Data are available upon reasonable request. For inquiries about data sharing, please send request at sailing1980@126.com.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors report no conflict of interest pertinent to this manuscript.

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