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Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

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Abstract

Background: Recent large high-quality trials have questioned the clinical effectiveness of medical expulsive therapy using tamsulosin for ureteral stones.
Objective: To evaluate the efficacy and safety of tamsulosin for distal ureteral stones compared with placebo.
Design, setting, and participants: We conducted a double-blind, placebo-controlled study of 3296 patients with distal ureteral stones, across 30 centers, to evaluate the efficacy and safety of tamsulosin.
Intervention: Participants were randomly assigned (1:1) into tamsulosin (0.4 mg) or placebo groups for 4 wk.
Outcome measurements and statistical analysis: The primary end point of analysis was the overall stone expulsion rate, defined as stone expulsion, confirmed by negative findings on computed tomography, over a 28-d surveillance period. Secondary end points included time to stone expulsion, use of analgesics, and incidence of adverse events.
Results and limitations: Among 3450 patients randomized between September 1, 2011, and August 31, 2013, 3296 (96%) were included in the primary analysis. Tamsulosin benefits from a higher stone expulsion rate than the placebo (86% vs 79%; $p < 0.001$) for distal ureteral stones. Subgroup analysis identified a specific benefit of tamsulosin for the treatment of large distal ureteral stones (>5 mm). Considering the secondary end points, tamsulosin-treated patients reported a shorter time to expulsion ($p < 0.001$), required lower use of analgesics compared with placebo ($p < 0.001$), and significantly relieved renal colic ($p < 0.001$). No differences in the incidence of adverse events were identified between the two groups.
Conclusions: Our data suggest that tamsulosin use benefits distal ureteral stones in facilitating stone passage and relieving renal colic. Subgroup analyses find that tamsulosin provides a superior expulsion rate for stones >5 mm, but no effect for stones ≤5 mm.
Patient summary: In this report, we looked at the efficacy and safety of tamsulosin for the treatment of distal ureteral stones. We find that tamsulosin significantly facilitates the passage of distal ureteral stones and relieves renal colic.

1. Introduction

Medical expulsive therapy (MET) refers to the administration of drugs such as tamsulosin, an α-adrenoceptor antagonist, to relax the smooth muscle of the ureter and inhibit peristaltic activity [1,2]. The efficacy of tamsulosin has been evaluated in numerous randomized controlled trials (RCTs) [2–6], with several meta-analyses having been published [7–9]. In general, trials have supported the use of tamsulosin to achieve higher stone expulsion rates and lower analgesic requirements. In our previous study, we demonstrated a significant therapeutic benefit of tamsulosin, over nifedipine, for relieving renal colic and facilitating ureteral stone expulsion [10].

Nevertheless, several recently published high-quality and large RCTs have questioned the effectiveness of α-blockers to be ineffective for the management of ureteral stones [11,12]. The Spontaneous Urinary Stone Passage Enabled by Drugs (SUSPEND) trial established that neither tamsulosin nor nifedipine decreased the need for further treatment to achieve stone clearance in 4 wk compared with placebo [11]. Additionally, a phase III trial, which included multiple centers, reported no benefit of tamsulosin for patients with distal ureteral calculi with regard to spontaneous stone passage, time to stone expulsion, or analgesic requirement [12]. Interestingly, another RCT, using silodosin, provided evidence of a possible benefit of silodosin in patients with distal ureteral stones [13]. In addition, the 2017 European Association of Urology guidelines recommend the use of α-blockers for MET as one of the treatment options, in particular for (distal) ureteral stones >5 mm [14].

The contradictory results provided by meta-analyses of small RCTs versus the findings of large, multicenter trials have questioned the effectiveness of tamsulosin. To address this issue, we conducted a multicenter, randomized, double-blind, placebo-controlled trial, including 3296 distal ureteral stone patients with renal colic, across 30 centers in China, to evaluate the efficacy and safety of tamsulosin as medical expulsion therapy for distal ureteral stones.

2. Patients and methods

2.1. Study design and participants

This double-blind, randomized, placebo-controlled trial was designed by urologists from the Urolithiasis Group of the Chinese Urological Association and researchers at Astellas Pharma (the study sponsor and manufacturer of the placebo). Data were analyzed by investigators at Tongji Hospital, Huazhong University of Science and Technology. The trial protocol and the informed consent form were approved by the

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Ethics Committee of Tongji Hospital. Our trial was performed across 30 centers in China, between September 2011 and August 2013. It was prospectively registered with the Chinese Clinical Trial Registry (ChiCTR-TRC-11001339). This trial was conducted in accordance with the Declaration of Helsinki and reported based on the Consolidated Standards for Reporting Trials statement.

A total of 3296 eligible patients were recruited from the outpatient departments of participating centers, using the following inclusion criteria: adults, 18–60 yr; emergency admission for renal colic; presence of a single ureteral stone confirmed by plain abdominal radiography (kidney–ureters–bladder), urinary ultrasonography, and/or noncontrast computed tomography (CT); a stone in the distal ureter, with a dimension of 4–7 mm; and a unilateral presentation. The distal ureter stone location was defined as below the level of the sacroiliac joint on CT, stone size was defined by the largest diameter in three planes, and all were determined by the reporting radiologist from CT imaging. The exclusion criteria included the following: fever; urinary tract infections; severe hydronephrosis; renal insufficiency, defined by an estimated glomerular filtration rate of $<$60 ml/min per 1.73 m^2; abnormal anatomy, such as a solitary kidney, horseshoe kidney, or a duplex urinary system; urethrostenosis; a history of ureter strictures; diabetes mellitus; hypotension (systolic blood pressure $<$100 mmHg); known or suspected pregnancy; current use of α-adrenoceptor antagonists or corticosteroids; and a previous history of ipsilateral ureteral surgery, spontaneous stone expulsion, or known or suspected allergy to the study medications.

2.2. Randomization and masking

Participants were randomly assigned in a 1:1 ratio to receive tamsulosin or placebo. Randomization and double blinding were performed according to the randomization sequence, which was produced with a computer-generated program by an independent statistician who had no further involvement in the study until the study analysis. Sequentially numbered study e-packs were securely stored at each study center using a password-protected computer database and were known only to the trial designer and statistician. The investigator, participants, care providers, and those assessing outcomes were blinded to treatment assignment throughout the trial, as the randomization list was generated by an independent statistician and was not available until the study analysis. The following stratification factors were used for analysis: age, sex, stone side, and stone size. All randomly assigned patients were included in the efficacy and safety analysis. Neither the specific researchers nor the patients had knowledge of group allocation, with the two different capsules having the same appearance and taste.

2.3. Procedures

The prescription for the two groups was as follows: two capsules of tamsulosin 0.2 mg or placebo, taken daily until spontaneous stone passage, up to a maximum of 28 d or the need for intervention. At the beginning of the enrollment and at every follow-up visit, each patient received his/her allocated trial medication for the next 7 d. Participants were requested to undergo a noncontrast CT weekly over the 28-d surveillance period of the trial. Participants were instructed to drink 2 l water per day and to collect the urine stone after urine filtration using a sieve. Additionally, the patients were authorized to use pain relief therapy with a 50 mg sodium diclofenac suppository on demand. Participants were asked to stop taking their medication use if stones were passed over the course of treatment. Baseline demographic and clinical data were collected before randomization in each local center. Patients were provided with diary cards to record any reactions to the prescribed drug or placebo.

For patients with a stone-free ureter on the final abdominal CT, in whom stone expulsion had occurred unconsciously, the date of the last positive stone status was recorded. Unsuccessful stone expulsion within 28 d was considered as a failed intervention. Discontinuation of trial medication and intervention prior to the end of the trial, due to uncontrollable pain, adverse events, or a patient's desire for stone removal, was also considered a failed intervention. These patients were included in the final analysis on an intention-to-treat (ITT) basis. Excluded from the analysis were patients who experienced stone expulsion prior to the start of the trial, those who withdrew their consent, or those who were lost to follow-up.

2.4. Outcomes

The primary end point was the stone expulsion rate, defined as stone expulsion, confirmed by negative findings on CT, over the 28-d surveillance period. Secondary end points included time to stone expulsion, rate of use of pain relief therapy during treatment, average analgesic consumption for recurrent renal colic, and incidence of adverse events.

2.5. Statistical analysis

Our null hypothesis was an absence of an effect of tamsulosin, compared with placebo, on stone expulsion, and a higher stone expulsion rate for the tamsulosin than placebo group (86% vs 80%). At a power of 95% and a significant type I error rate of 0.01, a sample size of $\geq$3100 was required, with 1550 patients per group (tamsulosin and placebo), for chi-squared analysis. Considering a drop-out rate of 10%, 3450 patients were enrolled in the trial.

Sampled data were compiled in a database specific for the trial, with all analyses performed using Stata (version 13; StataCorp, College Station, TX, USA). A complete descriptive analysis of all variables was performed on an ITT basis. Discrete variables were reported as number (%) and continuous variable as a mean (standard deviation). The proportion of stone expulsion over the 28-d surveillance was calculated for each treatment group, and between-group differences in mean proportions and 95% confidence interval (CI) were evaluated. A preplanned subgroup comparison of the difference in the rate of passage for distal ureteral stones was performed to explore the possible effects of age, sex, stone side, and stone size. We performed a logistic regression analysis for binary outcomes.

3. Results

Of the 3450 patients, 1695 were randomized to the tamsulosin group and 1695 to the placebo group. After randomization, 94 patients withdrew during the treatment and follow-up phases, with 3296 patients included in the ITT analysis of the primary outcome (1642 in the tamsulosin group and 1654 in the placebo group; Fig. 1). Demographic and baseline characteristics were similar between the two groups (Table 1), including average stone size: tamsulosin, 5.8 mm, and placebo, 5.7 mm.

Tamsulosin benefits from a higher stone expulsion rate than placebo (86% vs 79%; $p < 0.001$; Table 2) for distal ureteral stones. Additionally, we performed subgroup analyses of tamsulosin for the treatment of distal ureteral stones in the primary end point of a spontaneous rate of stone passage, with stratification by age, sex, ureter side, and stone size. In the subanalysis, tamsulosin had a significant effect on larger stones compared with smaller stones; however, no subanalysis differences were seen with

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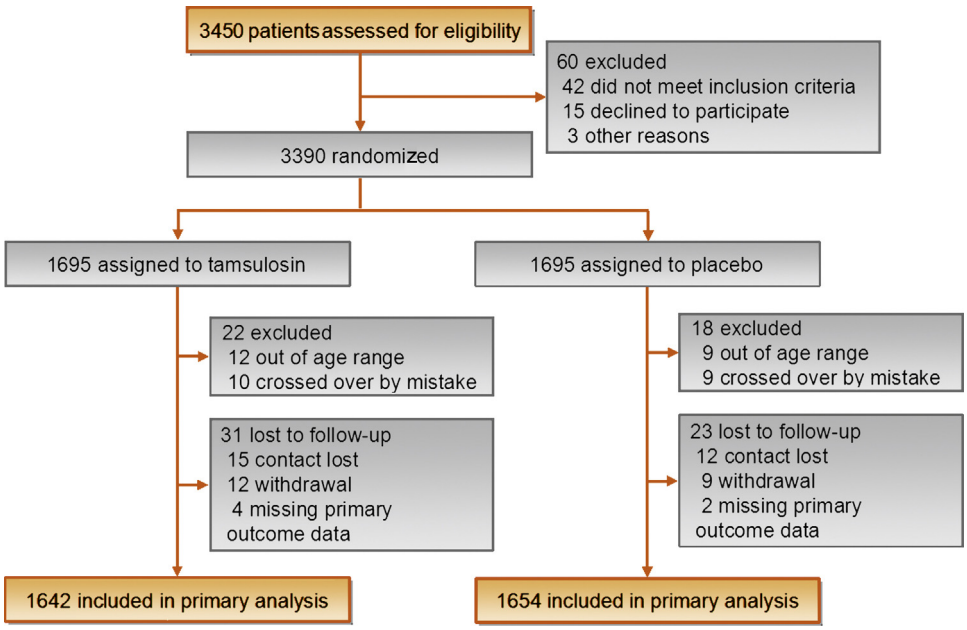

Fig. 1 – Trial profile.

Table 1 – Demographics and baseline characteristics of the study participants

Variable	Tamsulosin (n = 1642)	Placebo (n = 1654)
Age (yr)	40.1 (11.6)	40.7 (12.3)
Sex		
Male	556 (34%)	605 (37%)
Female	1086 (66%)	1049 (63%)
Stone size (mm)	5.8 (1.9)	5.7 (1.8)
Size distribution (mm)		
≤5	555 (34%)	561 (34%)
>5	1087 (66%)	1093 (66%)
Stone side		
Left	722 (44%)	761 (46%)
Right	920 (56%)	893 (54%)
Stone location		
Distal	849 (52%)	883 (53%)
Ureterovesical junction	793 (48%)	771 (47%)
History of previous stone episode	558 (34%)	541 (33%)
Duration of pain (d)	4.0 (3.8)	4.2 (4.0)
Antibiotic medication on admission	190 (12%)	170 (10%)

Data are presented as mean (standard deviation) or number (proportion).

respect to age, gender, and laterality (Fig. 2). We identified a specific therapeutic benefit of tamsulosin for large distal ureteral stones >5 mm (2.05, 95% CI, 1.64–2.54; $p < 0.01$; Fig. 2). No effect of tamsulosin, compared with the placebo, on the stone expulsion rate was identified for distal ureteral stones ≤5 mm (Fig. 2).

Considering the secondary end points, tamsulosin was also associated with a shorter time to expulsion for distal ureteral stones than the placebo (148.3 vs 248.7 h; $p < 0.001$; Table 2). Patients treated with tamsulosin reported less recurrent renal colic (1.9% vs 9.4%; $p < 0.001$; Table 2) and required fewer analgesics (89 vs 236 mg; $p < 0.001$; Table 2) compared with placebo. Adverse events were frequently reported; however, no significant difference of the adverse events was identified between the two groups (5.6% vs 5.1%; $p = 0.54$; Table 2). A summary of treatment-emergent adverse events is shown in Table 3.

4. Discussion

To the best of our knowledge, this study is the largest multicenter, prospective, randomized, double-blind, placebo-controlled trial to have investigated the efficacy of tamsulosin. We demonstrated that the use of tamsulosin was safe and clinically effective in patients with distal ureteral stones and renal colic. A subgroup analysis identified a specific clinical benefit of tamsulosin for

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Table 2 – Patient outcomes by treatment group

Outcome	Tamsulosin	Placebo	Difference (95% CI)	*p* value
All patients	(*n* = 1642)	(*n* = 1654)		
Stone expulsion rate, *N* (%)	1419 (86)	1300 (79)	7.8 (5.2–10.4)	<0.001
Average stone expulsion time (h)	148.3 ± 63.2	248.7 ± 76.6	−100.4 (−105.2 to −95.6)	<0.001
Average dosage of diclofenac (mg)	86 ± 32	236 ± 62	−150 (−153 to −147)	<0.001
Rate of pain relief therapy, *N* (%)	31 (1.9)	155(9.4)	−7.5 (−9.1 to −5.9)	<0.001
Side effect, *N* (%)	92 (5.6%)	84 (5.1%)	0.52 (−1.0 to 2.1)	0.5
Small stones (≤5 mm)	(*n* = 555)	(*n* = 561)		
Stone expulsion rate, *N* (%)	488 (88)	486 (87)	1.3 (−2.6 to 5.2)	0.5
Average stone expulsion time (h)	139.9 ± 68.9	147.1 ± 77.5	−7.20 (−15.80 to 1.40)	0.10
Average dosage of diclofenac (mg)	72 ± 31	168 ± 56	−95 (−100 to −90)	<0.001
Rate of pain-relief therapy, *N* (%)	6 (1.1)	40 (7.1)	−6.05 (−8.38 to −3.72)	<0.001
Side effect, *N* (%)	19 (3.5)	18 (3.2)	0.21 (−1.89 to 2.32)	0.8
Large stones (>5 mm)	(*n* = 1087)	(*n* = 1093)		
Stone expulsion rate, *N* (%)	931 (87)	814 (75)	11.17 (7.82–14.53)	<0.001
Average stone expulsion time (h)	152.5 ± 64.3	299.5 ± 79.2	−147.0 (−153.1 to −140.1)	<0.001
Average dosage of diclofenac (mg)	93 ± 35	270 ± 72	−177 (−182 to −172)	<0.001
Rate of pain relief therapy, *N* (%)	25 (2.3)	115 (11)	−8.22 (−10.28 to −6.16)	<0.001
Side effect, *N* (%)	73 (6.7)	66 (6.0)	0.68 (−1.37 to 2.73)	0.5

CI = confidence interval; OR = odds ratio, SD = standard deviation; WMD = weighted mean difference.
Data are mean (SD), number (%), WMD (95% CI), and OR (95% CI).

Table 3 – Adverse events by treatment group

Adverse event	Tamsulosin (*n* = 1642)	Placebo (*n* = 1654)	*p* value
Retrograde ejaculation	67 (4.1%)	48 (2.9%)	0.065
Dizziness	52 (3.2%)	50 (3.0%)	0.8
Headache	41 (2.5%)	46 (2.8%)	0.6
Fatigue	18 (1.1%)	15 (0.9%)	0.6
Nausea	43 (2.6%)	41 (2.5%)	0.9
Vomiting	38 (2.3%)	31 (1.9%)	0.4
Constipation	31 (1.9%)	28 (1.7%)	0.7
Diarrhea	21 (1.3%)	17 (1.0%)	0.5

Data are presented as number (proportion).

expulsion of distal ureteral stones >5 mm. Our findings add to the evidence of tamsulosin as a promising and useful treatment for large distal ureteral stones.

The effects of MET on pain relief were investigated based on evidence of the dominance of α-1-adrenoceptors in the smooth muscle of ureters and that blockade of these receptors can diminish the transmission of pain signals to the central nervous system [15,16]. Notably, our results demonstrated that tamsulosin significantly relieved renal colic; especially for patients with ureteral stones <5 mm, <50% of analgesics were needed in tamsulosin treatment compared with placebo. The benefits of MET for stone passage are thought to be mediated by a relaxation of the smooth muscles of the ureter via blockade of α-adrenergic receptors [17–19]. Physiologically, the highest concentration of α-1-adrenergic receptors is found in the distal segment of the ureter, therefore having the largest potential for a beneficial effect of α-blockers [20,21]. In alignment with findings from previously published RCTs [22], we identified a significantly higher rate of stone passage and lower time to expulsion with tamsulosin for distal ureteral stones, compared with placebo.

Two recently published RCTs by Pickard et al [11] and Furyk et al [12] reported no benefit of MET on the 4-wk reintervention rate or overall 28-d expulsion rate of ureteral stones, as well as distal ureteral stones specifically, calling into question the therapeutic application of MET. Our present study provides complementary information to these two trials. First, we chose the more conventional primary end point compared with the SUSPEND trial (28-d stone passage vs 4-wk reintervention rate). Pickard et al [11] compared the effectiveness of tamsulosin, nifedipine, and placebo on the rate of expulsion, defined as absence of surgical intervention at 4 wk after treatment initiation. They reported a comparable rate of expulsion for tamsulosin, nifedipine, and placebo use. However, the average stone sizes in Pickard et al's trial were 4.6, 4.5, and 4.5 mm for the tamsulosin, nifedipine, and placebo groups, respectively, and therefore, their trial was not powered to evaluate the effectiveness of MET for stones >5 mm. Furyk et al [12] reported no benefit of tamsulosin for patients with distal ureteric stones ≤10 mm. However, consistent with the findings of Furyk et al [12], our trial identified a benefit of MET for a stone size of >5 mm, but no effect for stones <5 mm. The average stone size in Furyk et al's trial was 4.0 mm for tamsulosin and 3.7 mm for placebo. Only 103 of 393 patients were enrolled in the subgroup analyses for large ureteral stones (5–10 mm), so the observed rate of larger ureteral stones is far less than that of the smaller ones. Of note, as both the RCT by Furyk et al [12] and that by Pickard et al [11] included patients with smaller ureteral stones, with an average stone size of <5 mm, both these trials contribute strong evidence for a lack of therapeutic benefit of MET for the treatment of ureteral stones <5 mm.

Several published meta-analyses regarding the therapeutic effectiveness of MET have reported a clinical benefit of the treatment. However, the evidence from these RCTs is limited, as these were small, single-center trials of low-to-moderate quality, with poor description of the measurement of outcomes and high between-trial variability. Moreover, very few trials used CT imaging to evaluate stone status [14]. Two meta-analyses evaluating the clinical

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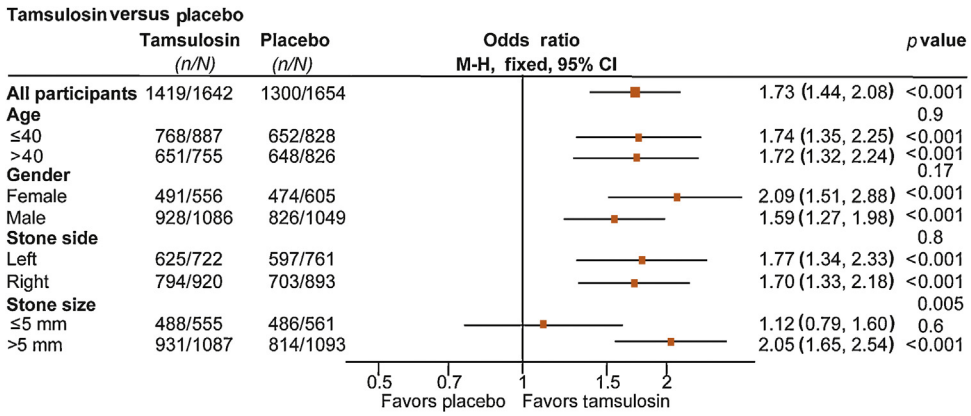

Fig. 2 – Subgroup analyses of the primary outcome in patients with distal ureteral stones. Interaction analyses showing the odds ratio (OR) and 95% CI for the primary outcome by subgroup: age, ≤40 versus >40 yr; sex, female versus male; stone side, left versus right; and stone size, ≤5 versus >5 mm. The graphs show the OR for each subgroup analysis of tamsulosin versus placebo. CI = confidence interval; M–H = Mantel–Haenszel.

outcomes of α-blockers reported passage rates of 53–90% [9] and 77–90% [23] compared with our passage rate of 86.4% for distal ureteral stones. In a recent study, Hollingsworth et al [7] performed a subgroup analysis stratified by stone size for all ureteral stone locations, identifying a specific benefit of α-blockers for larger stones. Patients with larger stones treated with an α-blocker had a 57% higher risk of stone passage compared with controls. Wang et al [24] pooled the data from 8 RCTs, showing a higher expulsion rate in patients with larger stones treated with tamsulosin compared with placebo. Although the results of Pickard et al [11] and Furyk et al [12] weakened the evidence of a therapeutic benefit of MET for stones ≤5 mm, there is still sufficient evidence to support the clinical use of MET for the management of ureteral stones >5 mm.

There are some limitations to this study. First, we used a standard dose of tamsulosin of 0.4 mg, which is the dose used in the western countries for the treatment of benign prostatic hyperplasia. Second, we observed patients suffering from a single ureteral stone with the largest dimension of 4–7 mm. It is important to note that our trial was primarily designed to detect a difference in the efficacy of tamsulosin among patients with relatively large ureteral stones. Finally, we should admit that severe hydronephrosis is an ambiguous exclusion factor that may introduce a bias to patient selection [13].

5. Conclusions

Our data suggest that tamsulosin significantly facilitates the passage of distal ureteral stones and relieves renal colic. Subgroup analyses find that tamsulosin provides a superior expulsion rate for stones >5 mm, but does not show any difference from placebo for stones ≤5 mm.

Author contributions: Hua Xu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Ye, Zeng, Z. Chen, H. Xu, H. Yang, He, Tang, X. Zhang, H. Li, W. Li, Wu, L. Chen, X. Chen, X. Liu, Deng, Pan, Xing, Wang, Cheng, Gu, Gao, J. Yang, Y. Zhang, Mi, Qi, J. Li, Hu, Liang, Sun, C. Xu, Long, Liao, S. Liu, G. Liu, X. Xu.

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Drafting of the manuscript: Ye, Zeng, Z. Chen, H. Xu, H. Yang.

Critical revision of the manuscript for important intellectual content: Ye, Z. Chen, H. Xu, He, Zeng.

Statistical analysis: Ye, Z. Chen, Zeng, H. Xu, H. Yang, Tang.

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