



Moxibustion for the treatment of ankylosing spondylitis: a systematic review and meta-analysis

Jiaojiao Hu, Yingying Mao, Yi Zhang, Ding Ye, Chengping Wen, Zhijun Xie

School of Basic Medical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, China

Contributions: (I) Study conception and design: All authors; (II) Administrative support: Z Xie; (III) Study inclusion and exclusion: J Hu, Y Mao; (IV) Collection and assembly of data: J Hu, Y Mao, D Ye; (V) Data analysis and interpretation: J Hu, Y Mao, C Wen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zhijun Xie, PhD. TCM Clinical Basis Institute, School of Basic Medical Sciences, Zhejiang Chinese Medical University, 548 Binwen Road, Hangzhou 310053, China. Email: xzj575@163.com.

Background: To systematically evaluate the efficacy of moxibustion in the treatment of ankylosing spondylitis (AS).

Methods: Seven electronic databases were systematically searched for relevant studies for inclusion from databases inception to December 31, 2018. Randomized controlled trials investigating the efficacy of moxibustion for AS treatment versus Western medicine (Wm) treatment were included for systematic review and meta-analysis. Effect estimates were pooled using the fixed or random-effects models. Between-study heterogeneity and publication bias were also assessed. Stratification analyses were further performed based on the treatment plan of experimental groups.

Results: Twenty-six studies were eligible for inclusion with a total of 1,944 AS patients. Meta-analysis showed that compared with those receiving Wm treatment alone, patients receiving moxibustion combined with Wm treatment or moxibustion alone had a higher clinical efficacy rate [odds ratio (OR) =4.21, 95% confidence interval (CI): 2.91 to 6.10, $P < 0.001$ for moxibustion combined with Wm versus Wm; OR =2.43, 95% CI: 1.62 to 3.65, $P < 0.001$ for moxibustion alone versus Wm]. In addition, patients receiving moxibustion combined with Wm treatment had lower levels of C-reactive protein [weighed-median difference (WMD) =-6.33, 95% CI: -9.64 to -3.01, $P < 0.001$] and erythrocyte sedimentation rate (WMD =-7.86, 95% CI: -11.26 to -4.46, $P < 0.001$) after treatment, respectively. Furthermore, moxibustion could also improve Schober test scores (WMD =0.85, 95% CI: 0.15 to 1.55, $P = 0.017$), occipital-wall distances (WMD =-0.55, 95% CI: -0.92 to -0.19, $P = 0.003$), and finger-ground distances (WMD =-3.64, 95% CI: -5.61 to -1.68, $P < 0.001$) of AS patients.

Conclusions: This study suggests that moxibustion is an effective complementary treatment for AS patients. However, further large-scale multicenter clinical trials are needed to confirm these findings.

Keywords: Ankylosing spondylitis (AS); moxibustion; meta-analysis; randomized controlled trial; systematic review

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Introduction

Ankylosing spondylitis (AS) is a chronic autoimmune inflammatory disorder with joint damage primarily to the joints of spine and the sacroiliac, leading to progressive bone

fusion of the spine (1). Nonsteroidal anti-inflammatory agents (NSAIDs), disease modifying antirheumatic drugs (DMARDs), glucocorticoid as well as biologic drugs are recommended as the principle treatments for AS patients (2). However, prolonged therapies with drugs such as NSAIDs

may have potential cardiovascular, gastrointestinal and renal risks (3). Therefore, substitution and complementary therapies have been actively searched to improve the treatment strategy for AS patients.

Moxibustion is one of the complementary and alternative therapies frequently used by patients with rheumatic diseases worldwide, especially in East Asian countries such as China. It is a form of heat therapy in which dried plant materials called “moxa” are burned on or near the surface of the skin. Several systematic review and meta-analyses have shown that moxibustion is effective in relieving rheumatic diseases such as rheumatoid arthritis and knee osteoarthritis (4,5). To date, there has been no critically designed systematic review assessing the efficacy and safety of moxibustion for the treatment of AS. A meta-analysis published in 2011 evaluated the effectiveness of moxibustion for major rheumatic conditions, however, only three trials related with AS were included (6). Therefore, in the present study, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the efficacy of moxibustion in the treatment of AS patients.

Methods

Data source and search strategy

This systematic review and meta-analysis were conducted adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement. The protocol of the present study was registered and approved by PROSPERO under the registration number of CRD42019104815. Briefly, seven databases including PubMed, Cochrane Library, EMBASE, China National Knowledge Infrastructure (CNKI), Wanfang, VIP Database for Chinese Technical Periodicals and China Biology Medicine (CBM) were systematically searched from databases inception through December 31, 2018. No restrictions were applied on language, year of publication or publication status. References of related articles were manually searched for potential eligible studies for inclusion.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion based on the following criteria: (I) randomized controlled trials; (II) participants are those diagnosed with AS; (III) studies comparing moxibustion alone or moxibustion combined

with Western medicine (Wm) to Wm alone for the treatment of AS patients. The exclusion criteria were: (I) observational or retrospective studies; (II) duplicated studies; (III) the control group was not treated with Wm alone; (IV) the experimental group used additional treatments (such as acupuncture, herbal therapy or rehabilitation).

Data extraction

Eligible studies were selected for detailed analysis and data extraction, which were performed by two investigators (JJ Hu and YY Mao). Disagreements were resolved through consensus. The following data were extracted from each study, which included first author, publication year, sample size, patient demographics, intervention measures in the experimental and control groups, outcome measurements and adverse events documented.

Assessment of risk of bias

We evaluated the quality of each study by using the Cochrane Risk of Bias tool (7), which consists of the following six items: (I) was the allocation sequence adequately generated? (II) was the allocation adequately concealed? (III) was knowledge of the allocated intervention(s) adequately presented during the study? (IV) were incomplete outcome data adequately addressed? (V) are reports of the study free of any suggestion of selective outcome reporting? (VI) was the study apparently free of other problems that could place it at risk of bias? Each item was classified into high (H), low (L), or unclear (U) risk of bias, respectively.

Data analysis

Statistical analyses were performed using Stata version 12.0 (Stata Corp LP, College Station, TX, USA). We used Cochrane's Q test and I^2 statistics to assess the magnitude of heterogeneity between studies (8,9). For dichotomous variables, odds ratios (OR) and 95% confidence intervals (CIs) were used, while for continuous variables, weighed-median difference (WMD) and 95% CIs were used. These effect estimates were combined using fixed-effects ($I^2 < 50\%$) or random-effects models ($I^2 \geq 50\%$) (10). Funnel plot was generated and publication bias was assessed using Egger's test. The trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of the results when publication bias existed. Stratification analyses

were further performed based on the treatment plan of experimental groups. P values of <0.05 were considered statistically significant.

Results

Study selection and participants characteristics

A flow chart of study inclusion and exclusion is shown in *Figure S1*. The initial screening yielded 1,176 articles, among which 26 studies (with data for 1,944 participants) were finally included. The included studies were published between 2002 and 2018 and originated in China. The median trial duration was 8 weeks. The sample size of included trials ranged from 24 to 220 participants. All the included trials used pure Wm as the control group. Eight trials used pure moxibustion in the experimental group (11-18), while 18 trials used moxibustion combined with Wm (19-36). The detailed information of the included studies is summarized in *Table 1*.

Risk of bias assessment

Twelve of the included trials reported appropriate sequence generation methods for the randomization process, while 14 trials were described as 'randomized'. None reported blinding because the blinding of participants and personnel was impossible to carry out in these studies. Almost every trial had high risk of bias according to the Cochrane risk of bias criteria (*Table S1*).

Clinical efficacy

The efficacy rate of the experimental group was 3.32 times of the pure Wm group (OR =3.32, 95% CI: 2.53 to 4.36, $P<0.001$) with no statistically significant between-study heterogeneity observed ($I^2=0\%$). The funnel plot was symmetric and no publication bias was detected using Egger's test ($P=0.337$). Stratification analysis showed that the efficacy rate was higher in the subgroup of moxibustion combined with Wm versus Wm alone (OR =4.21, 95% CI: 2.91 to 6.10, $P<0.001$) than in the subgroup of moxibustion alone versus Wm treatment alone (OR =2.43, 95% CI: 1.62 to 3.65, $P<0.001$) (*Figure 1*).

Axis functions

Compared with those receiving Wm treatment alone, the

experimental group using moxibustion combined with Wm had better improvements in Schober test (WMD =0.85; 95% CI: 0.15 to 1.55; $P=0.017$) (*Figure 2A*), occipital-wall distance (WMD =-0.55; 95% CI: -0.92 to -0.19; $P=0.003$) (*Figure 2B*), and finger-ground distance (WMD =-3.64; 95% CI: -5.61 to -1.68; $P<0.001$) (*Figure 2C*). However, no statistically significant improvements in chest expansion distance were observed between the two groups (WMD =-0.04; 95% CI: -0.29 to 0.21; $P=0.733$) (*Figure 2D*).

Inflammatory responses

Compared with the control group, the experimental group treated with moxibustion combined with Wm had lower levels of C-reactive protein (CRP) (WMD =-6.33, 95% CI: -9.64 to -3.01, $P<0.001$) (*Figure 3A*) and erythrocyte sedimentation rate (ESR) (WMD =-7.86, 95% CI: -11.26 to -4.46, $P<0.001$) (*Figure 3B*) after treatment, respectively. However, both CRP (WMD =7.73, 95% CI: -8.30 to 23.77, $P=0.344$) (*Figure 3A*) and ESR levels (WMD =3.79, 95% CI: -2.81 to 10.39, $P=0.261$) (*Figure 3B*) did not differ significantly between the experimental group treated with moxibustion alone and the control group using Wm alone.

Adverse events

Ten trials reported adverse events during treatment. In the control groups, the most commonly recorded adverse events were nausea, anorexia, diarrhea and hepatic injury, while in the experimental groups, burn injury was the most commonly seen adverse event. Overall, the experimental groups had fewer adverse effects reported compared with the control groups (OR =0.33; 95% CI: 0.19 to 0.57; $P<0.001$) (*Figure 4*).

Discussion

The current systematic review and meta-analysis showed that AS patients treated with moxibustion had better improvements in axis functions and inflammatory responses but fewer adverse effects compared with the control groups treated with Wm alone, suggesting that moxibustion might be a useful complementary and alternative therapy for AS patients.

Our analysis suggested that moxibustion could improve spinal mobility and inflammatory responses, which was in line with current evidence showing the anti-inflammatory effects of moxibustion. An *in vivo* study using collage-

Table 1 Summary of randomized clinical studies of moxibustion for ankylosing spondylitis

First author [year]	Sample size	Intervention group (regimen)	Control group (regimen)	Main outcomes	Adverse events
Bai H [2018]	48/48	Snake moxibustion (1 session =20–40 min, 3/week, total 2 weeks; n=48), plus (B)	Drug therapy (SASP; 1 g, 2/day; cloud G, injection, 1/day, total 2 weeks; n=48)	Response rate, ESR, CRP and BASMI	2/1
Lv MF [2018]	40/40	Snake moxibustion (1 session =30 min, 1/week, total 12 weeks; n=40), plus (B)	Drug therapy (etanercept, 50 mg, injection, 1/week, total 12 weeks; n=40)	Response rate	NR
Sun DP [2018]	28/27	Snake moxibustion (1 session =NR, 1/week, total 8 weeks; n=28), plus (B)	Drug therapy (ibuprofen, 300 mg, 3/day, total 8 weeks; n=27)	Response rate, ESR and CRP	NR
Yang SQ [2018]	41/41	Snake moxibustion (1 session =NR, 1/2week, total 4 weeks; n=41), plus (B)	Drug therapy (thalidomide, first week: 25 mg, 1/day; second week: 25 mg, 3/day; third week: 50 mg, 2/day; fourth week: 50 mg, 3/day; total 4 weeks; n=41)	Response rate	NR
Zhang YG [2018]	46/46	Medicinal moxibustion (1 session =30 min, 5 consecutive days/week; n=46), plus (B)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 3/day; third week: 0.75 g, 3/day; continue to 12 th week, total 12 weeks; n=46)	Response rate	3/10
Dong TT [2017]	30/30	Snake moxibustion (1 session =NR, 1/4 week, total 12 weeks; n=30), plus (B)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 2/day; third week: 0.5 g, 3/day; fourth week: 1 g, 2/day; continue to 12 th week, total 12 weeks; n=30)	Response rate, ESR, CRP, and VAS	NR
Li XC [2017]	37/35	Snake moxibustion (1 session =NR, 1/2 days, total 4 weeks; n=37), plus (B)	Drug therapy (etanercept 25 mg, injection, 1/day, total 4 weeks; n=35)	Response rate, ESR, CRP and BASMI	NR
Ma YS [2017]	30/30	Snake moxibustion (1 session =120–180 min, 1/week, total 3 weeks; n=30), plus (B)	Drug therapy (NSAIDs; MTX, 15 mg, 1/week, total 3 weeks; n=30)	Response rate, VAS and CRP	NR
Meng QL [2017]	30/30	Snake moxibustion (1 session =NR, total 12 weeks; n=30), plus (B)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 3/day; third week: 1 g, 2/day; continue to 12 th week, total 12 weeks; n=30)	Response rate, ESR, CRP, VAS and BASMI	6/7
Ren XX [2016]	30/30	Snake moxibustion (1 session =NR, 1/2weeks, total 6 weeks; n=30), plus (B)	Drug therapy (SASP; 0.5 g, 2/day; aggravation, plus celecoxib, 0.2 g/day, total 12 weeks; n=30)	Response rate, VAS, BASDAI, BASFI, ESR, CRP and BASMI	2/3
Tao JT [2016]	55/56	Snake moxibustion (1 session =120 min, 1/week, 4 times/session, total 4 weeks; n=55)	Drug therapy (SASP; 0.5 g, 3/day; MTX, 7.5 mg, 1/week; diclofenac sodium SR, 50 mg, 3/day, TGP, 0.2 g, 3/day, total 4 weeks; n=56)	Response rate	0/3
Zhang XL [2016]	12/12	Snake moxibustion (1 session =30–60 min, 1/2 days, 5 times/session, total 4 weeks; n=12)	Drug therapy (SASP; 1 g, 2/day; total 4 weeks, n=12)	Response rate, ESR and CRP	NR
Luo F [2014]	30/30	Medicinal moxibustion (1 session =30 min, 5 consecutive days/week, total 12 weeks; n=30), plus (B)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 3/day; third week: 0.75 g, 3/day; continue to 12 th week, total 12 weeks; n=30)	Response rate, ESR, CRP, VAS and BASMI	1/4
Hu JG [2013]	30/30	Moxa (1 session =20–30 min, 1/day, total 12 weeks; n=30)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 2/day; third week: 0.75 g, 2/day; fourth week: 1 g, 2/day; plus meloxicam, 7.5 mg, 1/day, total 12 weeks; n=30)	Response rate, ESR and CRP	0/0

Table 1 (continued)

Table 1 (continued)

First author [year]	Sample size	Intervention group (regimen)	Control group (regimen)	Main outcomes	Adverse events
Zhang XC [2013]	25/25	Medicinal moxibustion (1 session =NR, 1/day, 10 times/session, rest for 2 days between sessions, total 7 weeks, n=25)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 3/day; third week: 0.75 g, 3/day; fourth week: 1 g, 3/day; diclofenac sodium SR, 75 mg, 2/day, 1 session =12 days, total 7 weeks, n=25)	Response rate and ESR	5/18
Zhou ZP [2013]	30/30	Snake moxibustion (1 session =NR, 1/2 weeks, 6 times/session, total 12 weeks; n=30), plus (B)	Drug therapy (SASP; 0.25 g, 3/day; celecoxib, 0.2 g, 1/day, total 12 weeks; n=30)	ESR, CRP and BASMI	1/3
Gao P [2012]	32/32	Medicinal moxibustion (1 session =NR, 1/2 weeks, total 8 weeks; n=32), plus (B)	Drug therapy (SASP; 1 g, 2/day, total 12 weeks; n=32)	Response rate, ESR and CRP	NR
Li AM [2012]	60/60	Medicinal moxibustion (1 session =60 min, 5 consecutive days/week, total 12 weeks; n=60), plus (B)	Drug therapy (SASP; first week: 0.75 g, 2/day; second week: 1 g, 2/day; continue to 12 th week, total 12 weeks; n=60)	Response rate, ESR, CRP and BASMI	NR
Zhang L [2012]	53/50	Snake moxibustion (1 session =30 min, 1/2 days, total 12 weeks; n=53), plus (B)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 3/day; third week: 0.75 g, 3/day; continue to 12 th week, total 12 weeks; n=50)	Response rate, ESR, CRP and BASMI	NR
Wang J [2011]	29/29	Snake moxibustion (n=29), plus (B)	Drug therapy (SASP; 0.5 g, 3/day; diclofenac sodium SR, 25 mg, 3/day, total 8 weeks; n=29)	Response rate, BASDAI and BASFI	NR
Li Y [2009]	28/28	Moxa (1 session =30 min, 1/2 weeks, total 2 weeks; n=28), plus (B)	Drug therapy (SASP; first week: 0.25 g, 3/day; third week: 1 g, 2/day, plus meloxicam table, 75 mg, 1/day; total 2 weeks; n=28)	Response rate, ESR, CRP and VAS	NR
Zuo ZJ [2009]	30/30	Snake moxibustion (1 session =NR, 1/week, total 12 weeks; n=30)	Drug therapy (SASP; 1 g, 2/day; aggravation, plus NSAIDs, total 12 weeks; n=30)	Response rate, VAS, BASDAI, BASFI, ESR and CRP	1/3
Zhu XM [2009]	39/36	Snake moxibustion (1 session =NR, 1/4 weeks, 3 times/session, total sessions NR; n=39)	Drug therapy (SASP; first week: 0.25 g, 3/day; second week: 0.5 g, 2/day; third week: 0.5 g, 3/day; fourth week: 1 g, 2/day; n=36)	Response rate	NR
Zhang WY [2009]	112/108	Snake moxibustion (1 session =NR, 1/4 weeks, 3 times/session, total sessions NR; n=112)	Drug therapy (meloxicam table, 7.5–15 mg, 1/day, n=108)	Response rate	NR
Wan J [2008]	23/23	Snake moxibustion (1 session =NR, 1/2 weeks, rest for 2 weeks between sessions, total 12 weeks; n=23), plus (B)	Drug therapy (SASP; 1 g, 2/day; leflunomide, 20 mg, 1/day; Celebrex, 0.2 g, 2/day, total 12 weeks, n=23)	Response rate, ESR and CRP	NR
He YH [2002]	30/30	Snake moxibustion (1 session =NR, total 8 weeks; n=30)	Drug therapy (SASP; 75 mg, 3/day, total 8 weeks; n=30)	Response rate	NR

BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; BASMI, Bath ankylosing spondylitis measures index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MTX, methotrexate; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; SASP, salicylazosulfapyridine; TGP, total glucosides of Paeonia; VSA, visual analogue scale.

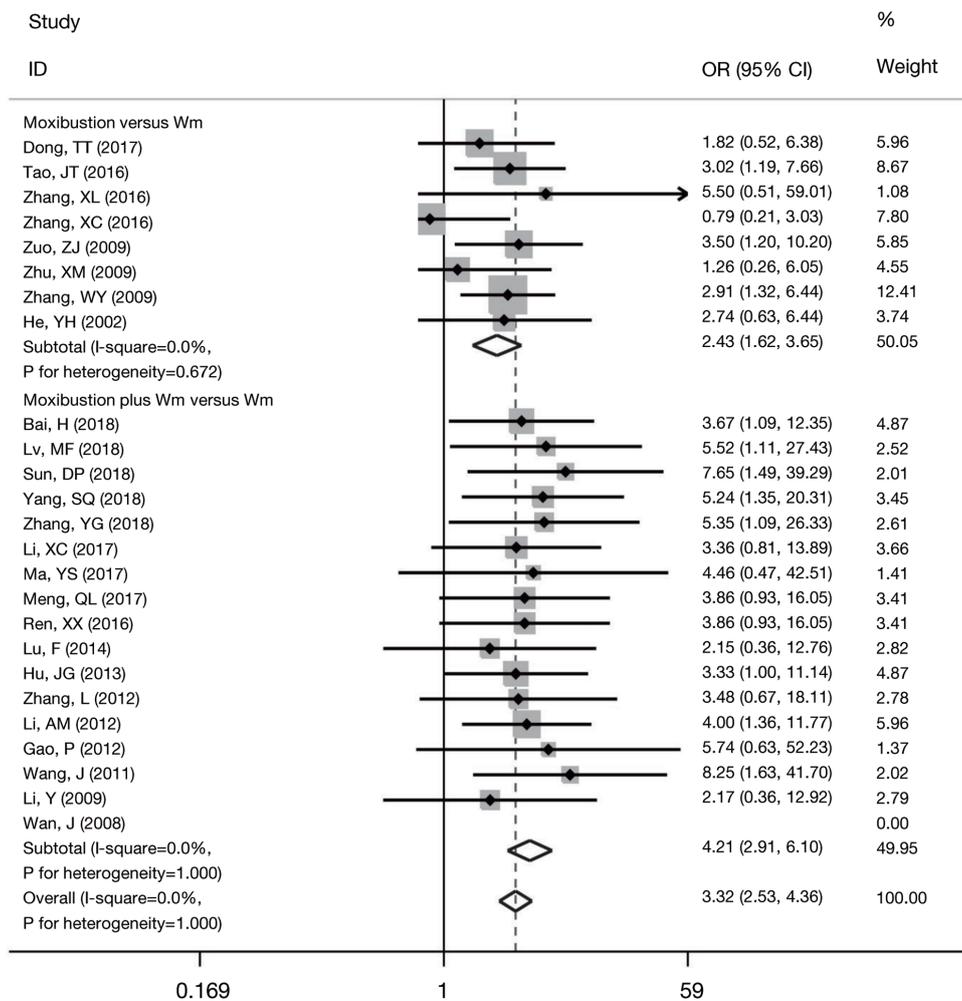
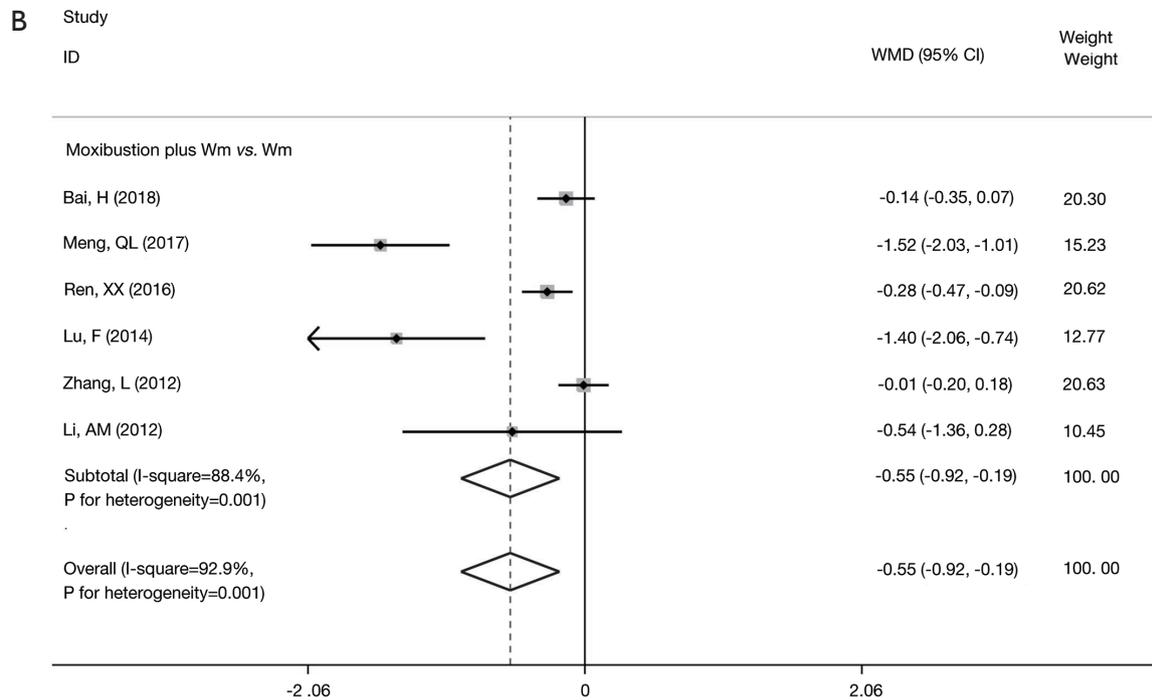
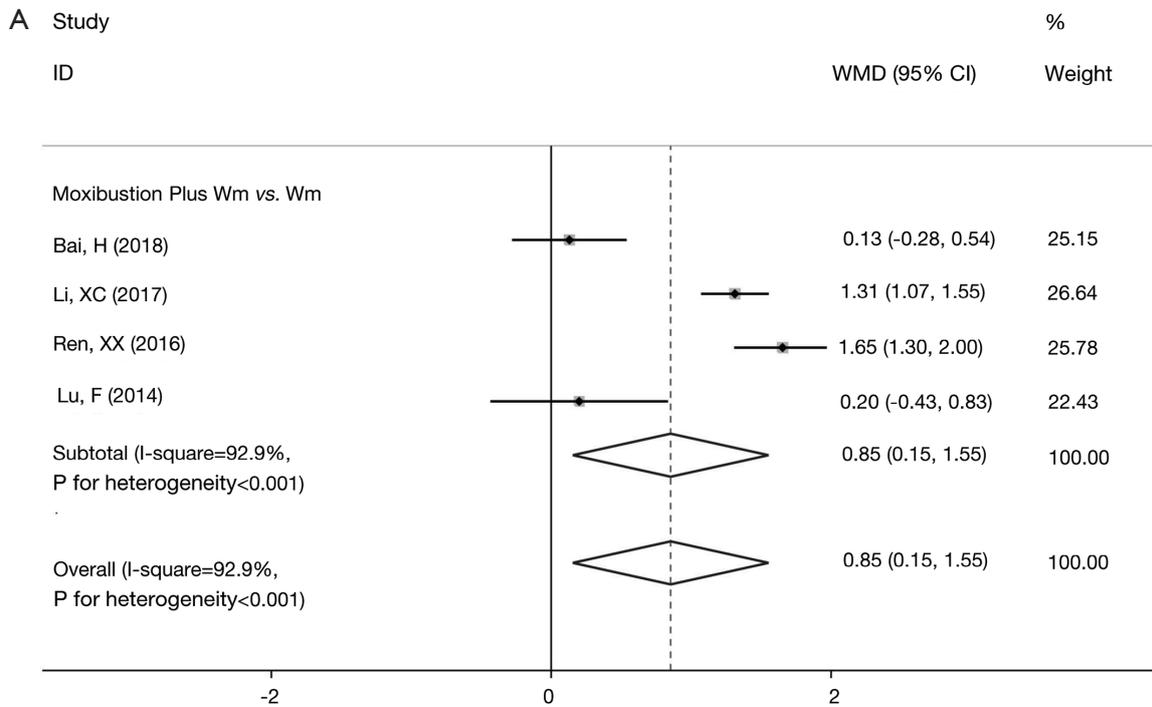


Figure 1 Forest plot of the clinical efficacy of moxibustion versus western medicine alone in the treatment of patients with ankylosing spondylitis.

induced arthritis (CIA) mouse model reported that the serum levels of interleukin (IL)-6 were significantly lower in the moxibustion treated group compared with untreated controls (37). The anti-inflammatory effect of moxibustion might be also related with the regulation of Treg cell number in spleen and the altered expression of Foxp3 and NF- κ B (38). As entheses-associated changes are the primary lesions in AS, and inflammation at axial skeleton and sacroiliac may ultimately leads to restriction of spinal function (39); however, the widely used DMARDs of methotrexate (MTX) and salicylazosulfapyridine (SASP) have been reported to be beneficial effect to peripheral joints but have little effect on axial joints (40). Therefore, our findings clearly lend support to the use of moxibustion in the clinical management of patients with AS.

The merits and limitations to our study are worth mentioning. To the best of our knowledge, this is the first meta-analysis to evaluate the efficacy of moxibustion in the treatment of patients with AS. Furthermore, our study included a total 26 studies with a relatively large number of AS patients. The major limitation of the current study was that the quality of the included studies was relatively low, with high risk of bias according to the Cochrane Risk of Bias tool. Only twelve trials reported the random sequence generation methods. None employed patient blinding and assessor blinding due to the particularity of moxibustion treatment. In addition, though no statistically significant between-study heterogeneity was observed for the primary endpoint “clinical efficacy”, we observed marked heterogeneity for the secondary endpoints such as



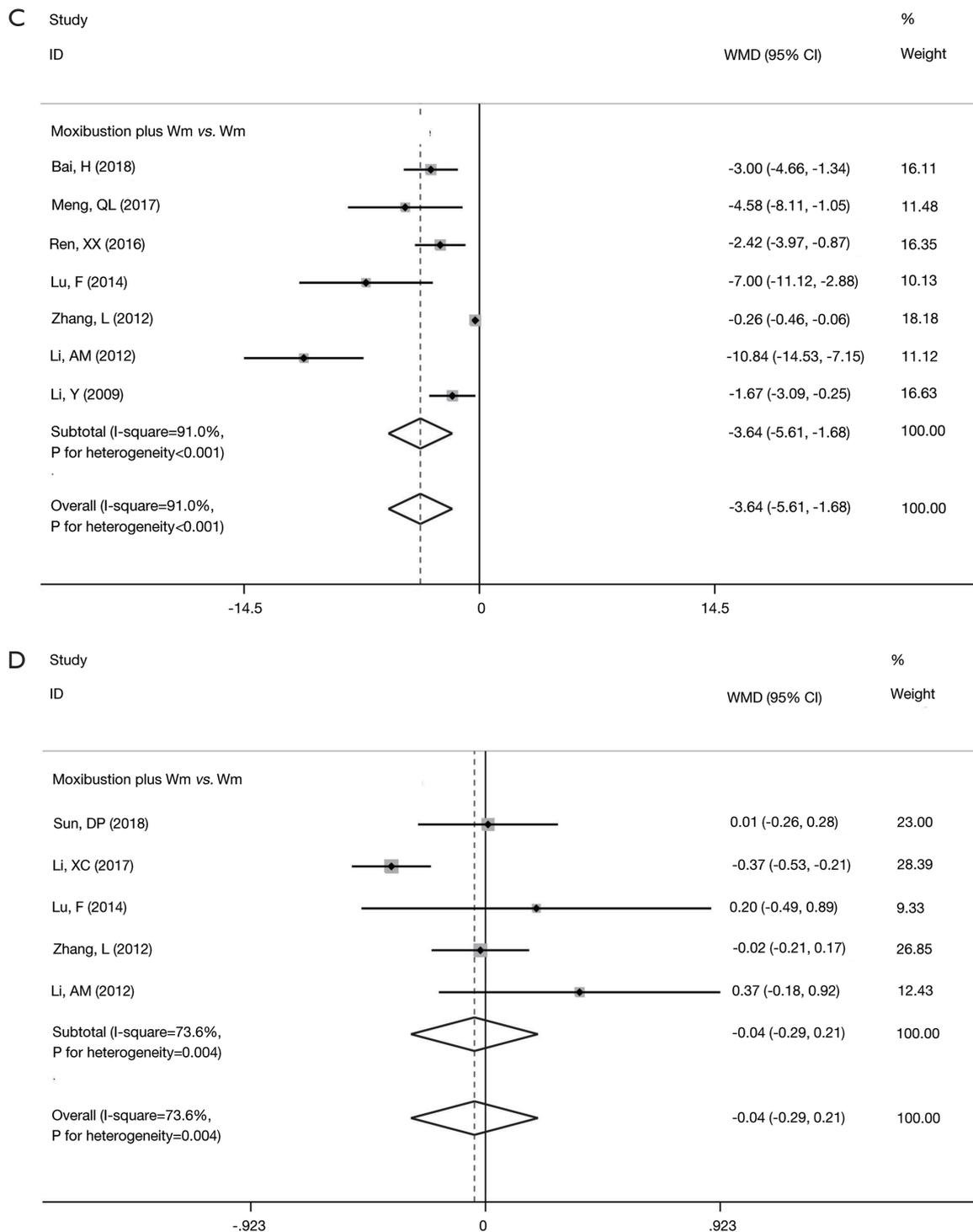


Figure 2 Forest plots of Schober test, occipital-wall distance, finger ground distance and chest expansion in patients with ankylosing spondylitis treated with moxibustion combined with western medicine versus western medicine treatment alone. (A) Schober test; (B) occipital-wall distance; (C) finger-ground distance; and (D) chest expansion.

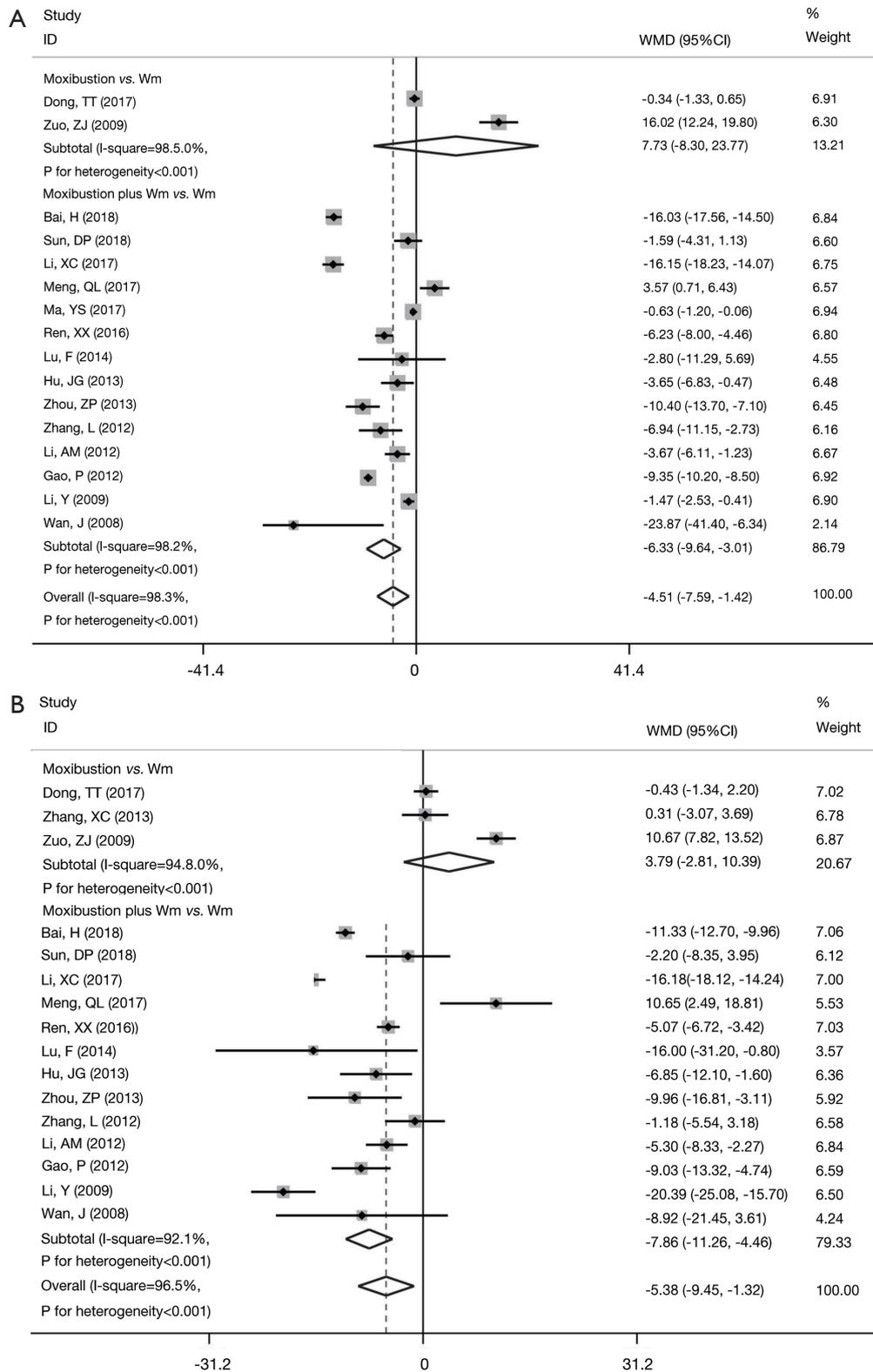


Figure 3 Forest plots of C-reactive protein and erythrocyte sedimentation rate in patients with ankylosing spondylitis treated with moxibustion combined with western medicine versus western medicine treatment alone. (A) C-reactive protein; and (B) erythrocyte sedimentation rate.

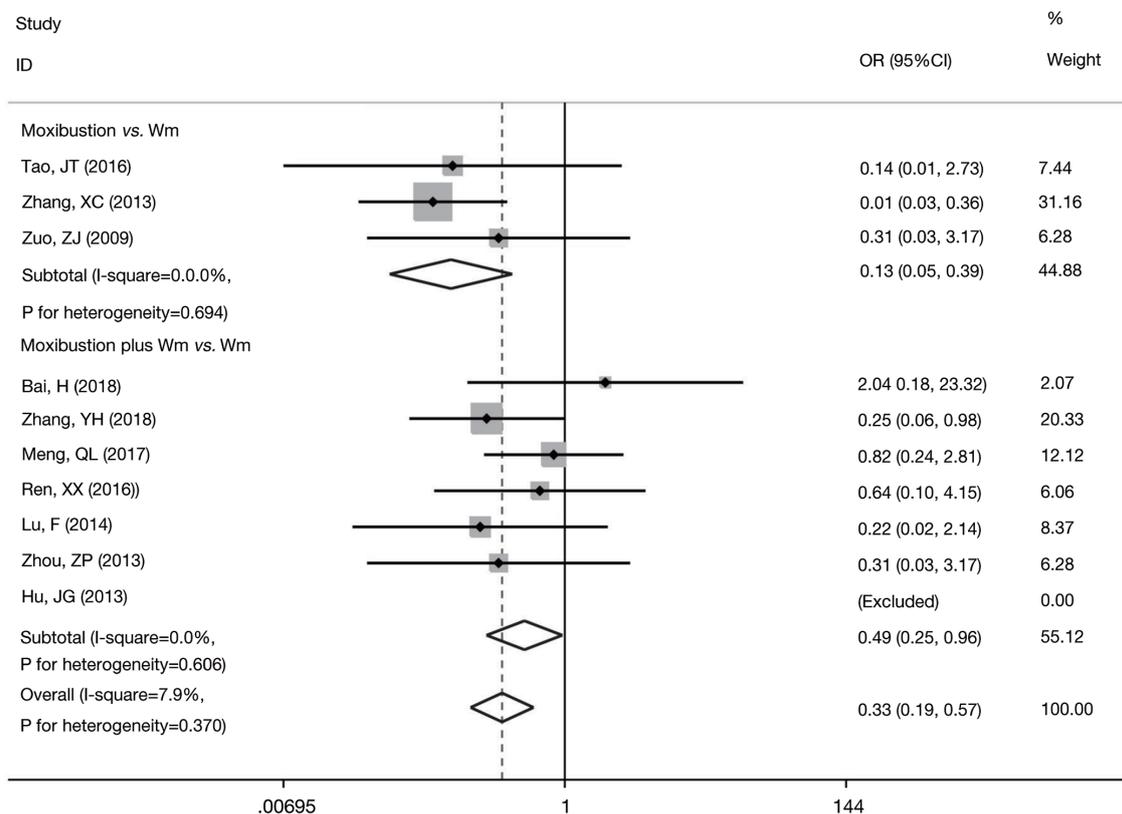


Figure 4 Forest plot of adverse events in patients with ankylosing spondylitis treated with moxibustion versus western medicine.

CRP, ESR and markers for axis functions. We performed stratification analyses as well as meta-regression, however, we did not detect contributing factors. The heterogeneity may be possibly related with the performances of the doctors, the quality of moxa made by Ay Tsao and others factor difficult to be controlled for in the trials. Furthermore, as treatment duration of the included studies were from 2 to 12 weeks, with a median duration of 8 weeks, the long-term efficacy of moxibustion in the treatment of AS remained to be further explored. In the future, large-scale multicenter RCTs with better design are warranted to validate the findings of the current study.

Conclusions

Our study suggested that moxibustion was an effective complementary treatment for AS patients, especially in terms of improving spinal mobility and inflammatory responses. However, further large-scale trials with better design are needed to confirm these findings.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm.2020.02.31>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The protocol of the present study was registered and approved by PROSPERO under the registration number of CRD42019104815.

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Supplementary

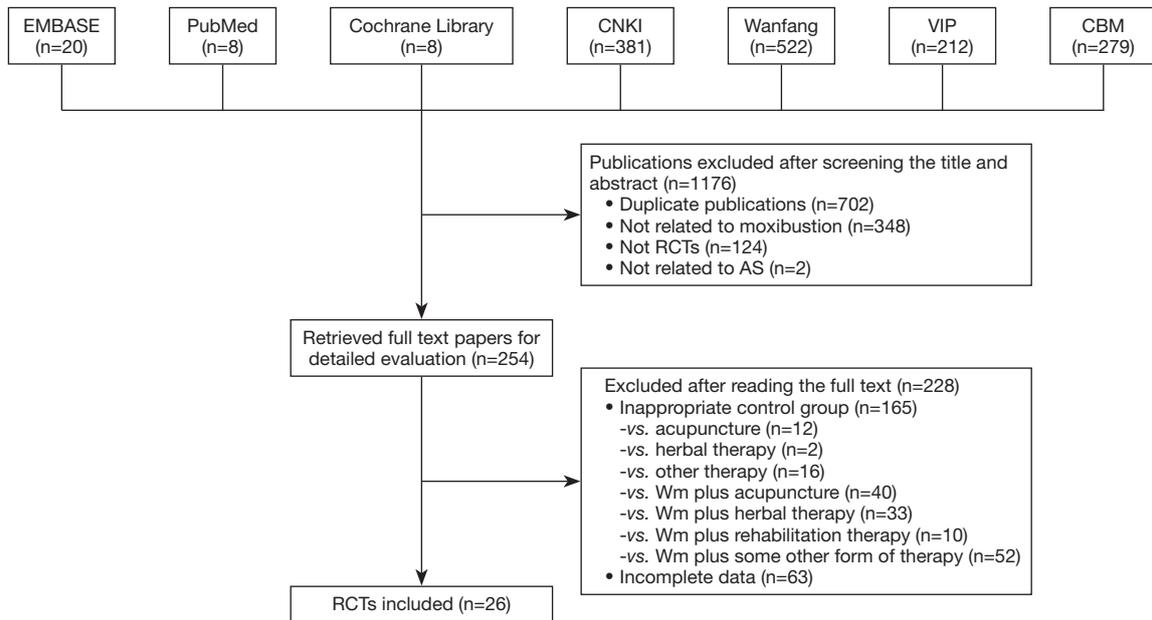


Figure S1 Flow diagram of study inclusion and exclusion.

Table S1 Quality assessment of included randomized controlled trials

First author [year]	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome data assessment	Incomplete outcome data	Selective reporting
Bai H [2018]	H	U	H	U	L	L
Lv MF [2018]	L	U	H	U	L	L
Sun DP [2018]	L	U	H	U	L	L
Yang SQ [2018]	L	U	H	U	H	L
Zhang YG [2018]	H	U	H	U	L	L
Dong TT [2017]	H	U	H	U	L	L
Li XC [2017]	H	U	H	U	L	L
Ma YS [2017]	H	U	H	U	L	L
Meng QL [2017]	H	U	H	U	L	L
Ren XX [2016]	L	U	H	U	L	L
Tao JT [2016]	L	U	H	U	L	L
Zhang XL [2016]	L	U	H	U	L	L
Luo F [2014]	L	U	H	U	L	L
Hu JG [2013]	L	U	H	U	L	L
Zhang XC [2013]	H	U	H	U	L	L
Zhou ZP [2013]	L	U	H	U	L	L
Gao P [2012]	H	U	H	U	L	L
Li AM [2012]	L	U	H	U	L	L
Zhang L [2012]	H	U	H	U	L	L
Wang J [2011]	H	U	H	U	L	L
Li Y [2009]	H	U	H	U	L	L
Zuo ZJ [2009]	L	U	H	U	L	L
Zhu XM [2009]	L	L	H	U	L	L
Zhang WY [2009]	H	U	H	U	L	L
Wan J [2008]	H	U	H	U	L	L
He YH [2002]	H	U	H	U	L	L

Note: H, L, and U represents high risk, low risk, and unclear, respectively.