

# Traditional Chinese Medicine For HIV-Associated Acute Herpes Zoster: A Systematic Review And Meta-Analysis of Randomized Trials

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## Research Article

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# Abstract

**Background:** Herpes zoster (HZ) is a common infection in individuals with immunocompromised immune systems, such as Acquired Immune Deficiency Syndrome (AIDS) patients. Traditional Chinese Medicine (TCM) has been used widely in clinical practice for HZ, which remains not supportive from evidence. This systematic review aimed to evaluate the effectiveness and safety of TCM in treating HIV-associated HZ.

**Methods:** Eight electronic databases, including CNKI, Wanfang, VIP, SinoMed, WHO ICTRP, CENTRAL, PubMed, and clinicaltrials.gov, were searched for randomized controlled trials (RCTs) testing TCM in treating HIV-associated HZ. Data were extracted on citations, study design, interventions, and outcomes. Cochrane risk of bias tool 2.0 were used for quality evaluation. We performed meta-analyses by Revman 5.3 software. Effect estimates were presented as risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data with their 95% confidence interval (CI).

**Results:** Twelve RCTs (644 patients) were included, majority of them had high or unclear risk of bias in terms. The result of meta-analysis showed that, pain intensity (VAS 0-5) in Chinese herbal medicine (CHM) group was lower than it in drugs group (MD=-0.87, 95%CI [-1.69, -0.04], 2 trials, n=93). Duration of herpes related pain (days) of patients in combination group was shorter than those in drugs group (MD=-9.19, 95%CI [-16.73, -1.65], n=144). The incidence of postherpetic neuralgia (PHN) in combination group was lower than it in drugs group (RR = 0.49, 95% CI [0.25, 0.99], n=202). As for cure rate (defined as complete absence of pain and herpes), 2 trials showed that CHM was better than drugs (RR = 1.58, 95% CI [1.13, 2.22], n=93), 5 trials showed combination treatment was better than drugs (RR = 1.40, 95% CI = [1.08, 1.82], n=224). Cure rate in acupuncture group was more improved than that in drugs group (RR=1.99, 95%CI=[1.18, 3.36], n=120). Four trials reported adverse effects which found no serious adverse events occurred.

**Conclusion:** Chinese herbal medicine and acupuncture demonstrate more benefits than drugs in relieving pain, improving cure rate and reducing incidence of PHN for HIV-associated HZ. However, given to the limited data and various TCM therapies, the conclusions need to be verified in future trials.

## Background

Acquired Immunodeficiency Syndrome (AIDS) is an autoimmune disease caused by the human immunodeficiency virus (HIV). HIV destroys the human immune system, attacks helper T cells, infects B cells, and leads to a significant decrease in peripheral blood lymphocytes. Currently, highly active antiretroviral therapy (HAART) is widely used for HIV infection. The treatment can effectively inhibit the replication of HIV transcription, reduce AIDS mortality; however, during the treating progress, decreasing of CD4 + T cells, kidney and liver damage<sup>[1][2][3]</sup>.

Herpes zoster, an acute infectious skin disease caused by the varicella-zoster virus (VZV), usually occurs between the earlier HIV infection stage and the period of AIDS<sup>[4]</sup>. The virus invades and latent along the sensory nerve. When the body's immune function is weak, the latent virus replicates and spreads,

resulting in HZ [5][6]. For patients with AIDS, HZ is more likely occurring and bring great pain due to its positron neuralgia, which greatly affect the quality of life[7][8]. The main drugs recommended in China Guideline on the Diagnosis and Treatment of AIDS for HIV complicated with HZ include acyclovir, famciclovir, and valaciclovir[9]. But there are series of reports reminding that acyclovir may lead to renal damage[10], and the use of ganciclovir in the treatment of HZ may be controversial[11]. Due to intolerant pain, many patients seek traditional Chinese medicine (TCM) for relieving symptoms. The often used TCM therapies include herbal medicine (both topical use or oral taking), acupuncture, and cupping. Since there have been substantial amount of clinical studies published, we therefore, evaluated current clinical evidence from randomized trials on the effectiveness and safety of TCM in the treatment of HIV-associated herpes zoster.

## Methods

This meta-analysis was performed following the PRISMA 2020 guidelines for systematic reviews and meta-analyses[12].

### Inclusion/Exclusion criteria

#### *Study type*

Randomized controlled trials (RCTs) were included without restriction on language, publication type, or blinding.

#### *Participants*

Without restriction on age, race, and nationality. Patients in all age groups, with either HIV infection or diagnosed as AIDS patients and complicated with acute HZ will be the main inclusion criterion, with duration of HZ less than 3 weeks[13],

#### *Interventions*

Trials testing any type of TCM therapies such as Chinese herbal medicine (CHM) or acupuncture, moxibustion, cupping with or without drugs (e.g. antiviral drugs, neurotrophic drugs, painkillers, and other common symptomatic treatments) were included. Combination of different type of TCM therapies as experimental treatment was also included.

#### *Controls*

The controls included no treatment, placebo and drugs therapy. If there were any drug therapy in control group, it must stay the same as intervention group.

#### *Co-interventions*

If there were any co-interventions for HIV/AIDS, such as HAART or active antiretroviral therapy (ART), it should be same between control and intervention group.

### **Outcomes**

1) Primary outcomes: Pain intensity (VAS score, McGill score, duration of pain); incidence of postherpetic neuralgia (PHN); cure rate (defined as a complete absence of pain and herpes) and cure rate defined as: number of cured/total number \*100%)<sup>[14]</sup>;

2) Secondary outcomes: Quality of life (World Health Organization Quality Of Life - WHOQOL, Karnofsky Performance Status - KPS); adverse events.

### **Searching strategies**

Up to 23<sup>rd</sup> May 2021, we systematically searched the following electronic bibliographic databases: China National Knowledge Infrastructure (CNKI), Wanfang Database, Chong Qing VIP, SinoMed, PubMed, the Cochrane Library, WHO International Clinical Trial Registration Platform (WHO ICTRP) and ClinicalTrials.gov. The details of searching strategies are shown in Additional file 1.

### **Screening**

All retrieved trials were managed using NoteExpress software. Initial screening was carried out based on inclusion/exclusion criteria after reading article titles and abstracts. The full-text screening was acquired and checked for eligibility before included in final analysis. Two authors carried out back-to-back literature screening independently. Any disagreement was solved through discussions and consultation with a third author.

### **Data extraction**

The extracted data were: (1) basic characteristics of included trials (first author, research topic, year of publication, etc.); (2) diagnosis information; (3) inclusion and exclusion criteria; (4) baseline characteristics; (5) control and intervention details; (6) primary outcome and their definitions, measuring time points, follow-up, ; (7) risk of bias components.

### **Quality evaluation**

The methodological quality of including trials were evaluated by the risk of bias assessment tool 2.0 <sup>[15]</sup> developed by Cochrane Collaboration. This tool assess risk of bias from 5 domains: randomization process, intended interventions, missing data, outcome measurement, and selective reporting (valid/invalid). Only if there are 5 domains assessed as low, the overall risk as low, otherwise even 1 domain assessed as some concern/high, the overall risk will turn in some concern/high. And if there were 4 or more domains assessed as some concerns, the overall risk will turn in high.

Two authors (Y Jiang and RX Zheng) independently extracted data, assessed and verified the risk of bias. The results were cross-referenced, and any differences were resolved through discussion with the third author (J Li or JP Liu).

## Data analysis

Review Manager 5.3 software<sup>[16]</sup> was used for data pooling and statistical analysis. According to the inclusion criteria of intervention and control, trials were divided into four comparisons. Meta-analysis was conducted for each comparison according to different outcomes. Mean difference (MD) and 95% confidence interval (CI) were used for continuous outcomes, and relative risk (RR) was calculated with 95%CI for dichotomous outcomes.

The Cochran Q test and the  $I^2$  statistics were used to examine the heterogeneity across the trials. The random effects model was used to estimate the size of the combined effects in the meta-analyses.

If  $P < 0.1$  and the source of heterogeneity was unknown, descriptive analysis was used instead of meta-analysis. Subgroup analysis was used for moderate heterogeneity or higher ( $I^2 \geq 30\%$  but less than 75%)<sup>[17]</sup>. Sensitivity analysis was used to investigate the effects of random-effects model analyses on heterogeneous results and the effects of any hypothesis.

Due to the large variability of TCM and the different combination of TCM and drugs, ineradicable clinical heterogeneity of the treatment measures in the included studies, the random-effects model was used to combine the data. The related charts for meta-analysis should be carried out, such as forest plot and funnel plot.

## Results

### Study search

In total, 378 trials (320 in Chinese and 58 in English) were searched, of which 139 were excluded before screening due to duplication, 202 were excluded at titles-abstracts screening, 25 were excluded at full-text screening. Eventually, 12 trials were included in our review. The inclusion process and exclusion reasons of screening are shown in Fig. 1.

### Characteristics of the included trials

The general information of included trial is presented in Table 1. The trials were published between 2000 and 2014, and were conducted in China. The participants in the trials were mainly male, while only 3 trials were female dominated<sup>[18,21,28]</sup>. There were 644 participants, 348 in the control group and 196 in the intervention group. Only 1 trial<sup>[26]</sup> reported co-intervention as HAART, but with no further details.

According to the intervention and controls, trials were divided into three comparisons: (1) CHM vs. drugs (2 trials), (2) CHM + drugs vs. drugs (8 trials)<sup>[20-27]</sup>, and (3) acupuncture vs. drugs (2 trials)<sup>[28,29]</sup>.

The baseline information of patients in included trials is shown in the following Table 1.

TCM therapies contain oral taken herbal granules, herbal medicine for external use, Chinese herbal injection and acupuncture and/or moxibustion. drugs included antiviral agents, non-steroidal antipyretic and pain killers, neurotrophic agents, and pain killer with administration as injection, oral and external use (Table 2)

**Table 1 Characteristics of included trials on traditional Chinese medicine for herpes zoster**

trial ID	Sample I/C	Gender M/F	Age (years)	Treatment regimen	Duration	Outcomes
<b>CHM vs. drugs</b>						
Jiang F 2009 <sup>[18]</sup>	30/30	I: 19/11 C: 17/13	I: 41.3±7.1 C: 45.3±8.7	I: Longdan Xiegan granules + Ruyi Jinhuang paste external use  C: Acyclovir (0.2g /po. /5 times per day) + Acyclovir ointment external (q.s. /p.a.a. /bid. or tid.)	14d	Pain (VAS score);  Cure rate;  Adverse effects
Meng L 2006 <sup>[19]</sup>	15/18	I: 10/16 C: 11/18	I: 42.5±7.5 C: 47.7±9.2	I: Longdan Xiegan granules + Ruyi Jinhuang paste external  C: Acyclovir (0.2g /po. /5 times per day) + Acyclovir ointment external (q.s. /p.a.a. /bid. or tid.)	14d	Pain (VAS score); Cure rate;  Adverse effects
<b>CHM + drugs vs. drugs</b>						
Yu F 2013 <sup>[20]</sup>	36/36	55/17	I: 60.2 (50~81) C: /	I: Tanreqing injection + CHM wash lotion external + Acyclovir + Acyclovir ointment external + Diclofenac sodium and Carbamazepine (same as control)  C: Acyclovir (5~10(mg/kg) /5% GS 250ml vgtt. /q8h.) + Acyclovir ointment external (q.s. /p.a.a. /Unknown) + Diclofenac sodium and Carbamazepine (Discretion /Unknown /Unknown)	21d	Incidence of PHN; Cure rate;
Duan XW 2011 <sup>[21]</sup>	10/10	14/6	37.34±12.9	I: Longdan Xiegan granules + Valacyclovir (200mg /po. /bid.)  C: Valacyclovir (200mg /po. /bid.)	45d	Pain time (Days); Cure rate
Zeng L 2005 <sup>[22]</sup>	18/20	I: 6/12 C: 9/11	I: 44.6 (36~52)	I: Longdan Xiegan formula + Jidesheng Sheyao tablets (external) + Acyclovir+ Vitamin B1	7d	Cure rate

			C: 42.6 (28~50)	and VitaminB12 + Somedon (same as control)		
				C: Acyclovir (10mg/(kg) /ivgtt. /q8h) + Vitamin B1 and VitaminB12 (Unknown /po./ Unknown) + Somedon(p.r.n. /po./ Unknown)		
Liang FL 2012 <sup>[23]</sup>	30/30	41/19	67.2 [60~81]	I: Herbal gargle (external) + Acyclovir + Ibuprofen or Tramadol (same as control)	10-30d	Incidence of PHN; Cure rate
				C: Acyclovir (5~10mg/kg /ivgtt. /q8h.)+ Ibuprofen or Tramadol (p.r.n. /po./ Unknown)		
Wang Q 2014 <sup>[24]</sup>	35/35	I: 18/17  C: 18/17	45±2	I: (Longdan Xiegan formula or Bazhen formula) + Ganciclovir + Unknown AA for external use + Compound glycyrrhizin injection + BCG -PSN + vitaminB12 + Calamine (same as control)	14-21d	Pain time (Days);  Incidence of PHN;  Adverse effects
				C: Ganciclovir (0.5g/ivgtt. /q8h.)+ Unknown antiviral agent for external use (q.s. /p.a.a./ Unknown)+ Compound glycyrrhizin injection (40mL /5% GS. Unknown /Qd. 7times.)+ BCG -PSN (1mg /im. /qod. for 4times.)+ vitaminB12 (q.s. /po./ Unknown)+ Calamine(p.r.n. /p.a.a./ Unknown)		
Shao Z 2011 <sup>[25]</sup>	18/16	I: 17/1  C: 14/2	I: 35.78±7.605  C: 35.88±7.940	I: (Longdan Xiegan formula or Chushi Weiling formula) + Sanhuang wash lotion (external) + Valacyclovir + Acyclovir (same as control)	28d	Pain (VAS score);  Cure rate;  Quality of life (WHOQOL); Adverse effects
				C: Valacyclovir (300mg /po./ bid)+ Acyclovir (5- 10(mg/kg) /Unknown /q8h.)		

Pan HR 2010 <sup>[26]</sup>	10/10	I: 9/1 C: 6/4	I: 20~35: n=5 36~50: n=3 ≥51: n=2  C: 20~35: n=3 36~50: n=4 ≥51: n=3	I: (Longdan Xiegan formula or Chushi Weiling formula) + Sanhuang wash lotion (external) + Valacyclovir + Acyclovir (same as control)  C: Valacyclovir + Acyclovir (300mg /po./ bid)+ Acyclovir (5- 10(mg/kg) /Unknown /q8h.)	28d	Pain time (Days);
Wu JL 2011* [27]	76/41	I: 57/17  C: 29/12	I: 40.12 (26~68)  C: 38.98 (22~66)	I: (Longdan Xiegan formula or Chushi Weiling formula or other unknown formula) + Valacyclovir + Acyclovir (same as control)  C: Valacyclovir + Acyclovir (300mg /po./ bid)+ Acyclovir (5- 10(mg/kg) /Unknown /q8h.)	24d	Quality of life (WHOQOL)
<b>Acupuncture vs. drugs</b>						
Liu ZW 2013 <sup>[28]</sup>	30/30	I: 17/13  C: 16/14	I: 44±21  C: 46±18	I: Acupuncture + Thread- Moxa in Zhuang Folk Medicine + Jingwanhong burn ointment (external)  C: Nimesulide (0.1g/ p.o./ bid.)+ Valacyclovir (250mg/p.o/ tid.)+ Vitamin B1 (20mg/ po./ tid.)+ Ribavirin ointment external (q.s. /p.a.a./ qid.)	14d	Pain (VAS score);  Cure rate
Li M 2000 <sup>[29]</sup>	20/40	50/60	(20~50)	I: Moxibustion + Acupuncture(Blood- letting puncture + reducing acupuncture method; Encircling needling + Reducing acupuncture method; Transverse needling)  C: Acyclovir (200mg/p.o/ tid.) + Acyclovir external (q.s. /p.a.a./ tid.)	27d	Cure rate

Note: I: intervention group, C: control group, M: male), F: female, CHM: Chinese herbal medicine;

Cure rate of HZ (Cure: complete absence of pain and herpes; Cure rate: number of cured/total number x100%)

\*Wu JL2011 is the only trial reported co-intervention: HAART, with no further details.

Table 2  
Details of the TCM therapies of included trials

Study ID	Name of TCM therapy and delivery  (Dosage for 1 use /Usage /Frequency)	Composition of CHM
Jiang F 2009 <sup>[18]</sup>	<p>Longdan Xiegan granules: 6g /po. /tid.;</p> <p>Ruyi Jinhuang Paste (external): q.s. /p.a.a. /bid. or tid.</p>	<p><b>Longdan Xiegan granules:</b> <i>Gentianae Radix et Rhizoma</i> (Longdan), <i>Gardeniae Fructus</i> (Zhizi), <i>Scutellariae Radix</i> (Huangqin), <i>Bupleuri Radix</i> (Chaihu), <i>Rehmanniae Radix</i> (Shengdi), <i>Plant Aginis Semen</i> (Cheqianzi-with Hot salt frying), <i>Alismatis Rhizoma</i> (Zexie), <i>Aristolochia Manshuriensis</i> (Guanmutong), <i>Angelicae Sinensis Radix</i> (Danggui-with Hot alcohol frying), <i>Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle</i> (Zhigancao).</p> <p><b>Ruyi Jinhuang Paste (external):</b> <i>Trichosanthis Radix</i> (Tianhuafen), <i>Curcumae Longae Rhizoma</i> (Jianghuang), <i>Paeoniae Radix Alba</i> (Baizhi), <i>Atractylodis Rhizoma</i> (Cangzhu), <i>Arisaemants Rhizoma</i> (Tiannanxing), <i>Glycyrrhizae Radix et Rhizoma</i> (Gancao), <i>Rhei Radix et Rhizoma</i></p>
Meng L 2006 <sup>[19]</sup>	<p>Longdan Xiegan granules: 6g /po. /tid.;</p> <p>Ruyi Jinhuang Paste (external): q.s. /p.a.a. /bid. or tid.</p>	<p>Longdan Xiegan granules : (Same as Jiang F 2009)</p> <p>Ruyi Jinhuang Paste (external): (Same as Jiang F 2009)</p>
Yu F 2013 <sup>[20]</sup>	<p>Tanreqing injection: 20ml /5% GS 250ml ivgtt. /qd..</p> <p>CHM wash lotion: 1000~2000mL / p.a.a. for 20~25min /bid.</p>	<p><b>Tanreqing injection:</b> <i>Scutellariae Radix</i> (Huangqin), <i>Pulvis Fellis Ursi</i> (Xiongdanfen), <i>Capra Hircus Cornu</i> (Shanyangjiao), <i>Lonicerae Japonicae Flos</i> (Jinyinhua), <i>Fructus Forsythiae</i> (Lianqiao), etc. Excipients: Propylene Glycol.</p> <p><b>CM wash lotion :</b> <i>Sophorae Flavescentis Radix</i> (Kushen), <i>Rehmanniae Radix</i> (Shengdi), <i>Phellodendri Chinensis Cortex</i> (Huangbo), <i>Corydalis Rhizoma</i> (Yuanhu), (Duanmulu), (Wubeizi), <i>Lonicerae Japonicae Flos</i> (Jinyinhua), (Tufuling), <i>Taraxaci Herba</i> (Pugongying), <i>Alumen</i> (Baifan), <i>Alismatis Rhizoma</i> (Zexie), <i>Borneolum</i> (Bingpian).</p>
Duan XW 2011 <sup>[21]</sup>	<p>Longdan Xiegan granules: Unknown /po. /bid.</p>	<p><b>Longdan Xiegan granules :</b> <i>Gentianae Radix et Rhizoma</i> (Longdan), <i>Gardeniae Fructus</i> (Zhizi), <i>Scutellariae Radix</i> (Huangqin), <i>Bupleuri Radix</i> (Chaihu), <i>Rehmanniae Radix</i> (Shengdi), <i>Plant Aginis Semen</i> (cheqianzi-with Hot salt frying), <i>Alismatis Rhizoma</i> (Zexie), <i>Tetrapanacis Medulla</i> (Tongcao), <i>Glycyrrhizae Radix et Rhizoma</i> (Gancao), <i>Paeoniae Radix Rubra</i> (Chishao), <i>Toosendan Fructus</i> (Chuanlianzi), <i>Artemisiae Scopariae Herba</i> (Yinchen), <i>Lonicerae Japonicae Flos</i> (Jinyinhua).</p>

\*details of acupuncture and moxibusion are provided in Additional file 2.

Study ID	Name of TCM therapy and delivery  (Dosage for 1 use /Usage /Frequency)	Composition of CHM
Zeng L 2005 <sup>[22]</sup>	<p>Longdan Xiegan formula: elixiation / po./ bid.</p> <p>Jidesheng Sheyao tablets (external): Grind into powder and mix with water to make paste, q.s. /p.a.a./ q3h.</p>	<p>Longdan Xiegan formula: Unknown.</p> <p>Jidesheng Sheyao tablets (external): <i>Paridis Rhizoma</i> (Chonglou), <i>Scolopendra</i> (Wugong), <i>Euphorbiae Humifusae Herba</i> (Dijincao) and etc.</p>
Liang FL 2012 <sup>[23]</sup>	<p>Herbal gargle: add 500mL water boil to 250 mL elixiation / p.a.a. 20 ~ 25min/ bid.</p> <p>(Patients with Oral Herpes) 30–50 ml/ Garg.3 ~ 5min/ bid.</p>	<p><b>Herbal gargle:</b> <i>Sophorae Flavescentis Radix</i> (Kushen), <i>Rehmanniae Radix</i> (Shengdi), <i>Scrophulariae Radix</i> (Xuanshen), <i>Ophiopogonis Radix</i> (Maidong), <i>Adenophorae Radix</i> or <i>Glehniae Radix</i> (Shashen), <i>Gynostemma Pentaphyllum</i> (Jiaogulan), <i>Ilexasprella Radix</i> (Gangmeigen), <i>Coptidis Rhizoma</i> (Huanglian)</p>
Wang Q 2014 <sup>[24]</sup>	<p>Longdan Xiegan formula or Bazhen formula: elixiation /po. /bid.</p> <p>Ganciclovir: 0.5g/ivgtt. /q8h.</p>	<p><b>Longdan Xiegan formula:</b> <i>Gentianae Radix et Rhizoma</i> (Longdan), <i>Gardeniae Fructus</i> (Zhizi), <i>Scutellariae Radix</i> (Huangqin), <i>Bupleuri Radix</i> (Chaihu), <i>Rehmanniae Radix</i> (Shengdi), <i>Plant Aginis Semen</i> (cheqianzi-with Hot salt frying), <i>Alismatis Rhizoma</i> (Zexie), <i>Tetrapanacis Medulla</i> (Tongcao), <i>Polygoni Cuspidate Rhizome et Radix</i> (Huzhang), <i>Arneblae Radix</i> (Zicao), <i>Lonicerae Japonicae Flos</i> (Jinyinhua).</p> <p><b>Bazhen formula:</b> <i>Rehmanniae Radix Praeparata</i> (Shudi), <i>Codonopsis Radix</i> (Dangshen), <i>Atractylodis Macrocephalae Rhizoma</i> (Jiaobaizhu), <i>Angelicae Sinensis Radix</i> (Dangui), <i>Chuanxiong Rhizoma</i> (Chuanxiong), <i>Paeoniae Radix Alba</i> (Chaobaishao), <i>Saposhnikoviae Radix</i> (Fangfeng), <i>Poria</i> (Fuling), <i>Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle</i> (Zhigancao), <i>Polygoni Cuspidate Rhizome et Radix</i> (Huzhang), <i>Arneblae Radix</i> (Zicao), <i>Lonicerae Japonicae Flos</i> (Jinyinhua).</p>

\*details of acupuncture and moxibusion are provided in Additional file 2.

Study ID	Name of TCM therapy and delivery  (Dosage for 1 use /Usage /Frequency)	Composition of CHM
Shao Z 2011 <sup>[25]</sup>	Longdan Xiegan formula or Chushi Weiling formula: elixation half dose /po. /bid.  Sanhuang wash lotion: q.s. /po./ Unknown	Longda nxiegan formula: (Same as Duan XW 2011)  <b>Chushi Weiling formula:</b> <i>Atractylodis Rhizoma</i> (Cangzhu), <i>Atractylodis Macrocephalae Rhizoma</i> (Baizhu), <i>Toosendan Fructus</i> (Chuanlianzi), <i>Citri Reticulatae Pericarpium</i> (Chenpi), <i>Polyporus</i> (Zhuling), <i>Poria</i> (Fuling), <i>Alismatis Rhizoma</i> (Zexie), <i>Tetrapanacis Medulla</i> (Tongcao), <i>Coicis Semen</i> (Yiyiren), <i>Astragali Radix</i> (Huangqi), <i>Codonopsis Radix</i> (Dangshen), <i>Corydalis Rhizoma</i> (Yuanhu), <i>Scolopendra</i> (Wugong), <i>Glycyrrhizae Radix et Rhizoma</i> (Gancao).  <b>Sanhuang wash lotion:</b> <i>Phellodendri Chinensis Cortex</i> (Huangbo), <i>Portulacae Herba</i> (Machixian), Indigo Naturalis (Qingdai), Excipients: Sesame oil.
Pan HR 2010 <sup>[26]</sup>	Longdan Xiegan formula and Chushi Weiling formula: elixation /po. /bid.  Sanhuang wash lotion: q.s. /po./ Unknown	Longda nxiegan formula: (Same as Duan XW 2011, Shao Z 2011)  Chushi Weiling formula: (Same as Shao Z 2011)  Sanhuang wash lotion: (Same as Shao Z 2011)
Wu JL 2011 <sup>[27]</sup>	Longdan Xiegan formula or Chushi Weiling formula: elixation /Unknown /Unknown	Longda nxiegan formula: Unknown  Chushi Weiling formula: Unknown
	<b>method/ specifications/ retention time</b>	<b>Operating site /Acupoint selection*</b>

\*details of acupuncture and moxibusion are provided in Additional file 2.

Study ID	Name of TCM therapy and delivery  (Dosage for 1 use /Usage /Frequency)	Composition of CHM
Liu ZW 2013 <sup>[28]</sup>	<p>encircling needling / 0.38mm*25mm, 15°/ 20min</p> <p>Thread-Moxa/ 0.7mm*300mm /sparkle press acupoint for 2 ~ 3times</p> <p>Jingwanhong burn ointment: q.s. /po./ After Thread-Moxa</p>	<p><b>Acupuncture:</b> Surround needling for herpes periphery/ No-special acupoint.</p> <p>Thread-Moxa: For small herpes clusters/ Main acupoint: Ashi points; matching points: Zusanli (ST36, bilateral) and Guanyuan (RN4). After Thread-Moxa apply Jingwanhong burn ointment on herpes, for big herpes prick before applying. Composition of Jingwanhong burn ointment: Unknown.</p>
Li M 2000 <sup>[29]</sup>	<p>Regular moxibustion: unknown/ 31min</p> <p>Blood-letting puncture: three-edged needle/ several drop of blood</p> <p>reducing acupuncture method: 0.38mm*25mm, 15°/ 30min</p> <p>Encircling needling + Reducing acupuncture method: 0.38mm*25mm, 15°/ 30min</p> <p>Transverse needling: 0.38mm*25mm, 15°/ 30min</p>	<p><b>Moxibustion:</b> Herpes area/ No-special acupoint</p> <p>Blood-letting puncture: Healthy skin around herpes/ No-special acupoint.</p> <p>Reducing acupuncture method: Determined acupoint/ Fengchi (GB20), Quchi (LI11), Hegu (LI4), Taichong (LR3), Zusanli (ST36), Yinlingquan (SP9), Sanyinjiao (SP6).</p> <p><b>Encircling needling:</b> Healthy skin around herpes/Needling around herpes, each needle interval for 5cm / No-special acupoint.</p> <p><b>Transverse needling:</b> Inside herpes range /Needling on herpes lesion area, each needle interval for 5cm side by side / No-special acupoint.</p>

\*details of acupuncture and moxibustion are provided in Additional file 2.

## Methodological quality

Among 12 included trials, none of them had low risk of bias. Seven trials had some concern of risk of bias and the other five trials had high risk of bias. Details regarding downgrading are provided in Fig. 2. Although four studies<sup>[19,21,22,23,25,27]</sup> did not specify randomization, from the same group with the studies that did specify randomization<sup>[17,18,20,24,26]</sup>. Thus researchers identified these 10 trials with low risk of bias in Domain1. Due to no protocol registration, all trials were identified with some concern in Domain2. No trials reported missing data and the number of participants randomized was consistent with that in statistical analyses, thus all trials were identified with low in Domain3. No objective outcome were used in seven trials<sup>[17,18,24,25,26,27,28]</sup> and the outcome measurement is likely to be influenced by lack of blinding. Domain4 in seven trials<sup>[17,18,24,25,26,27,28]</sup> were identified with high. No registered protocol of the included trials was mentioned, so the authors determined to evaluate the selective bias of other trials with some concern. (Fig. 2). And the percentage figure for risk of bias is presented in Additional file 3.

## **Analysis of overall effects**

Data from ten trials were included in meta-analyses, focusing on five classes of outcomes, and the results are shown as follows.

### ***Pain***

Four trials from 3 comparisons reported pain score (VAS, scale of 1 to 5). One trial<sup>[27]</sup> showed pain in acupuncture and moxibustion combined with CHM (external use) was lower than that in drugs (MD -1.10, 95% CI [-1.70, -0.50]). Two trials<sup>[17-18]</sup> showed more significant pain relief in CHM group than in drugs group (MD -0.87, 95% CI [-1.69, -0.04]). One trial<sup>[25]</sup> showed no difference of pain relief between CHM wash lotion + drugs and drugs (MD=-0.47, 95%CI [-1.38, 0.44]) (Table 3).

Duration of pain: Five trials from 2 comparisons reported duration of pain, it showed a significant reduction in CHM + drugs group, of the duration of pain (MD -9.19 day, 95% CI [-16.73, -1.65], 4 trials), than in drugs group<sup>[20,23,24,25]</sup>. And in acupuncture and moxibustion + drugs group, the reduction of duration of pain was also more than it in drugs group (MD -5.87 day, 95% CI [-7.85, -3.89], 1 trial)<sup>[27]</sup>. (Table 3)

### ***Incidence of post-herpetic neuralgia***

Three trials<sup>[19,22,23]</sup> reported the incidence of PHN and showed benefit of CHM + drugs in reducing the incidence of PHN (RR 0.49, 95% CI [0.25, 0.99]), comparing with drugs. (Table 3)

### ***Cure rate of herpes zoster***

Nine trials exhibited significantly better cure rate in CHM, compared with drugs (RR 1.58, 95% CI [1.13, 2.22], 2 trials)<sup>[17,18]</sup>, better cure rate in CHM + drugs, compared with drugs (RR 1.40, 95% CI [1.08, 1.82], 5 trials)<sup>[19-22,24]</sup>, and better cure rate in acupuncture and moxibustion, compared with drugs (RR 1.99, 95% CI [1.18, 3.36], 2 trials)<sup>[27,28]</sup>. (Fig. 3)

### ***Quality of life***

Two trials <sup>[24,26]</sup> reported the quality of life, measured by the WHOQOL - 100, from 1 to 100 and it showed that CHM + drugs improved quality of life than drugs (MD = 4.72 scores, 95%CI [0.45, 8.98],) (Table 3).

Table 3  
Summary report of different outcomes and effect estimates

Comparison group	Outcomes	Study ID	Sample size I/C (Events)	Effect estimation [95%CI]	P ( $\alpha = 0.05$ )
CHM vs Drugs	Pain score (VAS)	<b>Total</b>	<b>45/48</b>	<b>MD -0.87 [-1.69, -0.04]</b>	<b>0.04</b>
		Jiang F 2009	30/30	MD -1.04 [-2.05, -0.03]	0.04
		Meng L 2006	15/18	MD -0.52 [-1.96, 0.92]	0.48
	Cure rate (end of treatment)	<b>Total</b>	<b>45/48 (35/23)</b>	<b>RR 1.58 [1.13, 2.22]</b>	<b>0.008</b>
		Meng L 2006	15/18 (11/9)	RR 1.38 [0.78, 2.43]	0.18
	Jiang F 2009	30/30 (24/14)	RR 1.71 [1.12, 2.62]	0.01	
CHM + Drugs vs Drugs	Pain score (VAS)	Shao Z 2011	18/16	MD -0.47 [-1.38, 0.44]	0.31
	Duration of pain (days)	<b>Total</b>	<b>73/71</b>	<b>MD -9.19 [-16.73, -1.65]</b>	<b>0.02</b>
		Duan XW 2011	10/10	MD -16.00 [-23.32, -8.68]	<0.0001
		Wang Q 2014	35/35	MD -1.70 [-2.80, -0.60]	0.003
		Pan HR 2010	10/10	MD -16.00 [-23.32, -8.68]	<0.0001
		Shao Z 2011	18/16	MD -5.46 [-10.89, -0.03]	0.05
	Incidence of PHN	<b>Total</b>	<b>101/101 (10/21)</b>	<b>RR 0.49 [0.25, 0.99]</b>	<b>0.05</b>
		Liang FL 2012	30/30 (3/9)	RR 0.33 [0.10, 1.11]	0.07
		Yu F 2013	36/36 (6/9)	RR 0.67 [0.26, 1.68]	0.39
		Wang Q 2014	35/35 (1/3)	RR 0.33 [0.04, 3.05]	0.33

Note: CHM (Chinese herbal medicine), AM (Acupuncture and moxibustion), MD (Mean difference), CI (Confidence interval), RR (Risk radio), PHN (Postherpetic neuralgia).

Comparison group	Outcomes	Study ID	Sample size I/C (Events)	Effect estimation [95%CI]	P ( $\alpha = 0.05$ )
	<b>Cure rate (end of treatment)</b>	<b>Total</b>	<b>112/112 (62/44)</b>	<b>RR 1.40 [1.08, 1.82]</b>	<b>0.01</b>
		Duan XW 2011	10/10 (10/6)	RR 1.62 [0.97, 2.69]	0.06
		Zeng L 2005	18/20 (10/8)	RR 1.39 [0.71, 2.73]	0.34
		Liang FL 2012	30/30 (10/8)	RR 1.25 [0.57, 2.73]	0.57
		Shao Z 2011	18/16 (11/4)	RR 2.44 [0.97, 6.17]	0.06
		Yu F 2013	36/36(21/18)	RR 1.17 [0.76, 1.79]	0.48
	<b>Quality of life (WHOQOL-100)</b>	<b>Total</b>	<b>94/57</b>	<b>MD 4.72 [0.45, 8.98]</b>	<b>0.03</b>
		Shao Z 2011	18/16	MD 7.59 [1.06, 14.12]	0.02
		Wu JL 2011	76/41	MD 3.07 [-1.55, 7.69]	0.19
AM vs. Drugs	<b>Pain score (VAS)</b>	Liu ZW 2013	30/30	MD -1.10 [-1.70, -0.50]	0.0003
	<b>duration of pain (days)</b>	Liu ZW 2013	30/30	MD -5.87 [-7.85, -3.89]	<0.00001
	<b>Cure rate (end of treatment)</b>	<b>Total</b>	<b>70/50 (46/16)</b>	<b>RR 1.99 [1.18, 3.36]</b>	<b>0.01</b>
		Liu ZW 2013	30/30 (18/11)	RR 1.64 [0.94, 2.85]	0.08
		Li M 2000	40/20 (28/5)	RR 2.80 [1.28, 6.14]	0.01
Note: CHM (Chinese herbal medicine), AM (Acupuncture and moxibustion), MD (Mean difference), CI (Confidence interval), RR (Risk radio), PHN (Postherpetic neuralgia).					

## ***Adverse effects***

Four trials reported adverse effects <sup>[17,18,23,24]</sup>.

Two trials compared CHM with drugs, and both treated intervention group with Longdan Xiegan granules + Ruyi Jinhuang Paste and control group with Acyclovir. One of them<sup>[17]</sup> reported no drug-related adverse

reaction, the other one<sup>[18]</sup> reported a few cases underwent the abnormal liver function, but not exact number, with no abnormal index in routine blood, urine, and kidney function test.

Two trials compared CHM + drugs with drugs. One trial<sup>[24]</sup> reported no drug-related adverse reaction. Intervention treatment of this trial was Longdan Xiegan formula or Bazhen formula + Ganciclovir + Unknown AA for external use + Compound glycyrrhizin injection + BCG -PSN + vitaminB12 + Calamineand, while the control group was treated with all same as intervention group except CHM. One trial<sup>[23]</sup> reported 3 cases of slightly dizzy (intervention group:2 cases, control group: 1 case), after first dose of intravenous antiviral drugs, but all of cases with no abnormal index in routine blood, urine, liver function and kidney function test. The intervention of this trial is with Longdan Xiegan formula or Chushi Weiling formula + Sanhuang wash lotion + Valacyclovir + Acyclovir, and the control is with Valacyclovir + Acyclovir.

## Discussion

### Main finding

16 trials of HIV-associated herpes zoster was found, but 4 trials focused on postherpetic neuralgia, only 12 RCTs (n = 644) focused on acute herpes zoster and were included in this review. Those trials representing both genders and covering all age. All trials were published between 2000–2014, and are conducted in China. CM treatment include oral taken granules of CHM, external use CHM, injection of CHM and Acupuncture and moxibustion. Due to the limitation and the small sample size of each included trials, we are not able to draw firm conclusions relating TCM therapy in treating patients with HIV-associated acute herpes zoster.

All trials Compared with drugs, CHM + extrenal use demonstrated positive effects in improving cure rate and alleviating pain (VAS). CHM + drugs is much better than drugs on improving cure rate, shortening the duration of pain, reducing the incidence of PHN, improving cure rate and quality of life (WHOQOL-100) at the end of treatment. Acupuncture and Moxibustion demonstrated positive effects in alleviating pain (VAS), shortening the duration of pain, and improving cure rate at the end of treatment. Four included trials reported outcome of adverse events, two reported non-serious adverse events.

### Comparison with other studies

The correlative factor for HIV -associated HZ is usually around hypoimmunity and immunosuppression, which are hard to fix. Compared with drugs, four systematic reviews suggested positive effects of TCM therapy. Wet cupping<sup>[30]</sup>, Longdancao (*Gentiana scabra Bunge*.)single herb formula<sup>[31]</sup> and acupuncture<sup>[32]</sup>may decrease the rate of PHN. Acupuncture using independently<sup>[31]</sup> and Acupuncture plus moxibustion<sup>[33]</sup> may reduce VAS score of pain. *Gentiana scabra Bunge*. Formula (Longdancao single herb formula) could also shorten the pain duration<sup>[34]</sup>.

The clinical significance of those study results are yet to be established, and high-quality evidence with rigorous research methods is still insufficient.

## Limitations

The measures of the control group of integrative medicine were inconsistent, which might be because of the unregulated drug use. And the number of included trials and the number of sample sizes were small, the trial scale was limited, and the general quality was low. Most of the included trials did not describe in detail of the specific randomization method, did not use the blind method, and the evaluation of outcome indicators mostly consisted of doctor evaluation or patient self-rating scale, which was highly subjective. Therefore, the results of meta-analysis can only indicate the partial effect of CHM and AM on HIV-associated HZ, and the reliability of the conclusions obtained is limited.

## Implications for Clinical Practice and Further Research

Our review suggests that TCM may be a potentially alternative therapy for the treatment of HIV-associated HZ, but most of the included trials have modified the original formula regimen of CHM. Therefore, clinicians should add and subtract some herb according to physical signs in clinical practice to better improve clinical symptoms.

The included trials were limited by the small sample size and relatively low methodological quality. We hope that in the future, with the support of a more rigorous methodology, more multi-center clinical trials of CHM treatment of HIV/AIDS-associated HZ will be carried out with large sample size, especially RCT trials. More high-quality evidence will help to verify the effectiveness of CM and integrative medicine treatment, and provide more reliable support for this clinical problem.

In terms of basic research, the research on the components of CHM, the effective mechanism of acupuncture and moxibustion therapy, and the interaction between Chinese and drugs still need to be further explored, so as to provide an experimental basis for clinical research on this topic.

## Conclusion

Low certainty of evidence showed that Chinese herbal remedy and acupuncture may be beneficial in relieving pain for HIV-associated HZ, and appears to be safe. Further research with higher quality of evidence is still needed before clinical recommendation of TCM therapies.

## Abbreviations

HZ: herpes zoster ; HIV: human immunodeficiency virus; CNKI: China National Knowledge Infrastructure; TCM: Traditional Chinese Medicine; CHM: Chinese herbal medicine; PHN: Postherpetic neuralgia; RCTs: Randomized controlled trials; CI: Confidence interval; QOL: Quality of life; RR: Risk ratio; MD: Mean difference; I: intervention group, C: control group, M: male, F: female,

## Declarations

**Ethics approval and consent to participate**

Not applicable.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

Not applicable.

### **Competing interests**

The authors have no conflicts of interest to disclose.

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### **Authors' contributions**

YJ and JPL conceived the review. YJ performed the statistical analyses and wrote the draft of manuscript with interpretation and critical revision from all authors. YJ, RXZ and XWZ participate in data compilation. JL, ZYY and HDL systematically searched and selected the literature. SYQ and MH help with figure designing. MH, HJC and JPL revised the final manuscript. All authors read and approved the final manuscript.

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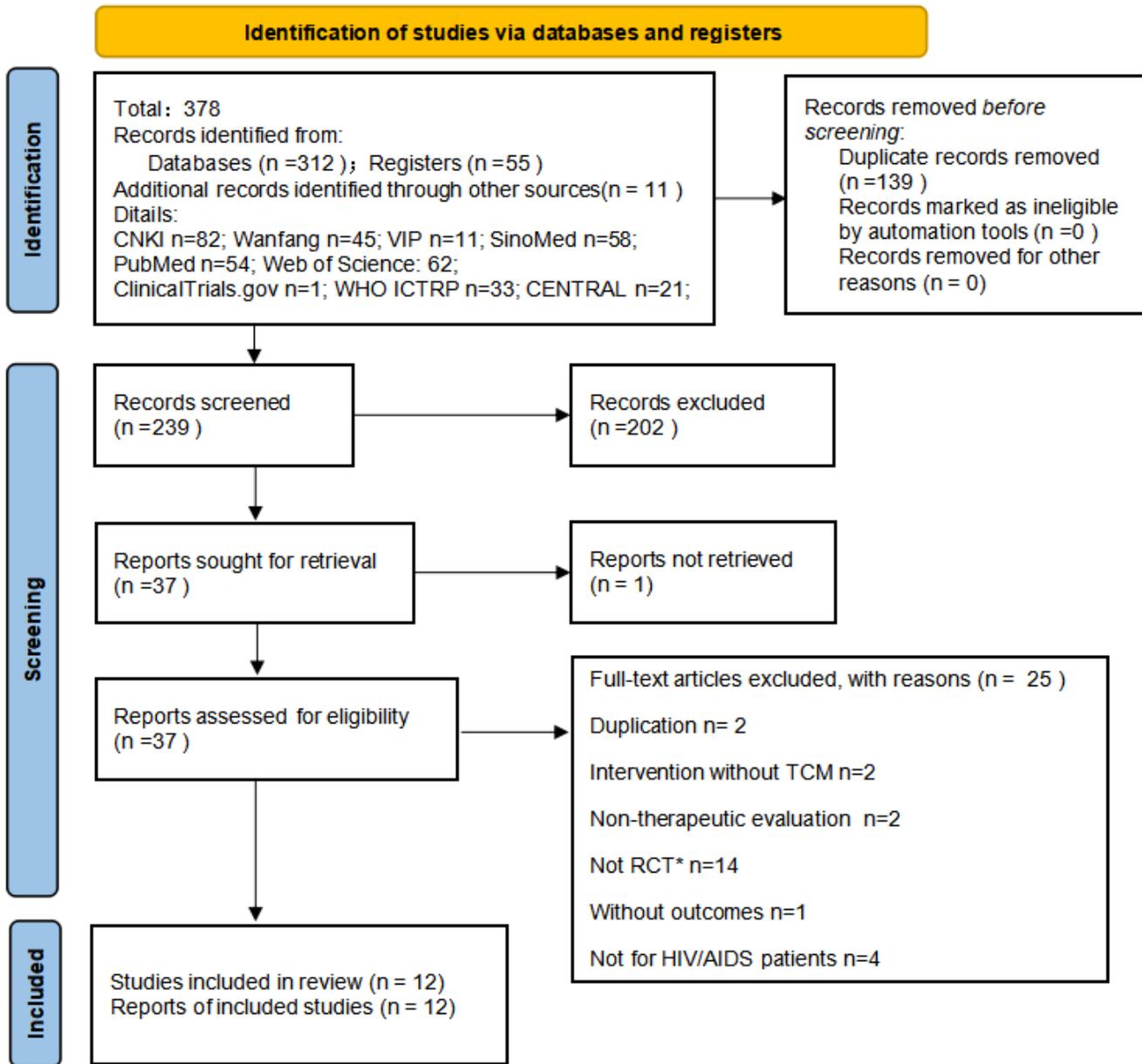
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## Figures



\*Studies that showed significant inconsistencies in describing the use of randomization and blinding methods were also considered not to be true RCTs.

**Figure 1**

Flowchart of study searches and screening Note: TCM (Traditional Chinese medicine)

Group	CHM vs. Drugs		CHM + Drugs vs. Drugs								AM vs. Drugs		Judgement:
	Study ID	Jiang F 2009	Meng L 2006	Yu F 2013	Duan XW 2011	Zeng L 2005	Liang FL 2012	Wang Q 2014	Shao Z 2011	Pan HR 2010	Wu JL 2011	Liu ZW 2013	
D1	+	+	+	+	+	+	+	+	+	+	+	+	?
D2	?	?	?	?	?	?	?	?	?	?	?	?	?
D3	+	+	+	+	+	+	+	+	+	+	+	+	+
D4	?	?	+	+	+	+	+	?	?	?	?	?	?
D5	?	?	?	?	?	?	?	?	?	?	?	?	?
Overall	!	!	!	!	!	!	!	?	?	?	?	?	?

Judgement:  
 ● High  
 ● Some concerns  
 ● Low

Domains:

D1: Bias arising from the randomization process

D2: Bias due to deviations from intended intervention

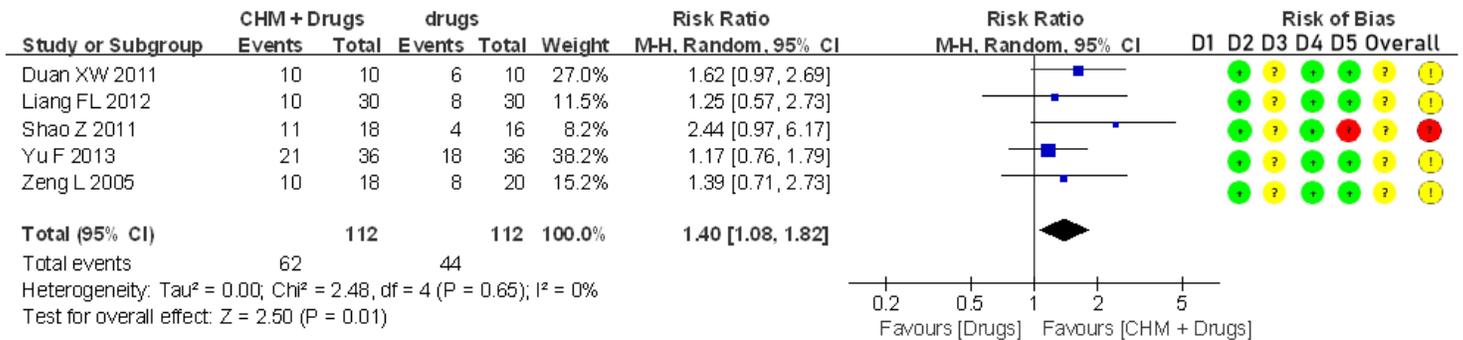
D3: Bias due to missing outcome data

D4: Bias in measurement of the outcome

D5: Bias in selection of the reported result

Figure 2

Risk of bias assessment of including trials using Rob2 tool



Risk of bias legend

Domains:

D1: Bias arising from the randomization process

D2: Bias due to deviations from intended intervention

D3: Bias due to missing outcome data

D4: Bias in measurement of the outcome

D5: Bias in selection of the reported result

Figure 3

Cure rate of HZ for CHM + drugs vs. drugs

## Supplementary Files

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