Review Article

Comparative effectiveness of East Asian traditional medicine for treatment of idiopathic short stature in children: Systematic review and network meta-analysis

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ABSTRACT

Background: Idiopathic short stature (ISS) is a common problem in children and causes many economic and social burdens. In Asian countries, East Asian traditional medicine (EATM) therapies are widely used for children with ISS. In this study, we compared and ranked various EATM therapies for the treatment of pediatric ISS using network meta-analysis.
Methods: Randomized controlled trials that evaluated various EATMs for pediatric ISS were found through searching 14 electronic databases. The primary outcome was growth velocity (GV). The comparative effectiveness of the treatments was ranked based on the surface under the cumulative ranking curve (SUCRA) and the risk of bias was assessed. The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations approach.
Results: Fourteen studies comprising 1,066 participants were included. HM plus GH showed statistically significant superiority over other EATM therapies including acupuncture (weighted mean difference (WMD) 3.20 cm, 95% confidence interval (CI) 0.40 to 5.99) and HM (WMD 3.70 cm, 95% CI 1.41 to 5.99) for improving GV per year, although there was no difference compared with GH alone (WMD 1.18 cm, 95% CI -0.27 to 2.63). SUCRA indicated that HM plus GH was the most effective therapy for increasing GV, followed by GH, HM plus acupressure, and HM. No serious adverse events were reported.
Conclusion: For the treatment of ISS, HM plus GH might have a large beneficial effect and might be a better option than EATM therapies and GH alone. However, more long-term, high-quality trials are warranted to confirm the findings.
Protocol registration: PROSPERO (https://www.crd.york.ac.uk/prospero/), CRD42020187160.

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1. Introduction

Idiopathic short stature (ISS) is a condition in which the individual's height is two standard deviations or more below the corresponding average height for a given age, sex, and population group, in the absence of any systemic, endocrine, nutritional, or chromosomal abnormality.[1] In children with short stature, a number of potential causes, such as true growth hormone (GH) deficiency and Turner syndrome, must be considered. If these condi-tions are not identified as the underlying cause, ISS can be diagnosed. Approximately 80% of children with short stature are estimated to have ISS.[2] Recombinant human GH was approved for ISS treatment by the US Food and Drug Administration in 2003[3]; however, it requires daily parenteral administration and is expensive because it is not covered by health insurance in most countries.[4–6] Although other therapeutic alternatives such as aromatase inhibitors, metformin, and insulin-like growth factor-1 (IGF-1) have been employed for the treatment of ISS, there is no gold standard treatment thus far and the management of ISS remains controversial.[7]

East Asian traditional medicines (EATMs) including acupuncture, moxibustion, herbal medicine (HM), and qigong have been widely used for the treatment and prevention of various diseases

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for thousands of years and are regarded as proper complementary and alternative medicines worldwide. Even among children that grow up in similar environments, Asian children may be smaller than Caucasian children.[8] This has led parents in many Asian countries including Korea to use EATM treatments for their children's growth. According to a retrospective study in 2016, growth disorder was the most common chief complaint among children and adolescents who visited the department of Korean Pediatrics in a Korean Medicine Hospital.[9] Several pre-clinical and clinical studies have indicated that EATM therapies have potential benefits for the treatment of ISS.[10–12] However, comparative studies on the effectiveness of EATM therapies have not been conducted thus far and the lack of evidence from direct comparisons between EATMs makes it difficult for clinicians to find the most effective therapies in clinical settings. Further, the lack of analysis regarding the comparative effectiveness and safety of these therapies makes it difficult to compare the advantages of different EATM therapies, which presents an obstacle for the efficient distribution of medical resources.

Network meta-analysis (NMA) is a method for assessing the comparative effectiveness of multiple treatment strategies by evaluating direct and indirect evidence.[13] In addition, it can provide the ranks of various treatment modalities according to their effectiveness, which can be useful for decision making in clinical settings[13] as well as for healthcare policy makers.[14] Therefore, this study aimed to summarize and evaluate the comparative effectiveness and safety of EATM therapies for ISS treatment in children through a systematic review and NMA.

2. Methods

The protocol for this study has been registered on the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020187160) and Open Science Framework (OSF, URL: https://osf.io/s4vp7) Registries. We reported the study according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) extension statement incorporating NMAs for healthcare interventions.[15]

2.1. Eligibility criteria

We included only the studies that met the following study design, participant, treatment, and control intervention criteria.

(1) Type of study design: parallel-design randomized controlled trials (RCTs).
(2) Type of participant: children with ISS (a height more than two standard deviations below the corresponding average height for a given age, sex, and population) without other diseases that can cause short stature such as GH deficiency, regardless of sex or race.
(3) Type of treatment intervention: EATM therapies including acupuncture, HM, moxibustion, cupping therapy, qigong, Tai Chi, pharmacopuncture, bee venom, chuna, meditation, a combination of these therapies, and a combination of interventions in the treatment and control groups (ex. HM plus GH as treatment interventions).
(4) Type of control intervention: placebo, no medical treatment (lifestyle guidance such as exercise and sleep guidance), EATM therapies, or conventional treatment (such as GH). For combination therapy groups, there were no limits on the number of combined interventions used for the treatment and control groups since multiple interventions are used in actual clinical settings.
(5) Type of outcome measures: The primary outcome measure was growth velocity (GV) (rate of change in height) during the follow-up period. We determined our primary outcome as GV under the consensus of researchers and experts because it is a more sensitive measure of growth than time-specific height measures.[16]

The secondary outcome measures were (1) other growth-related anthropometric indicators post-treatment such as height, predicted adult height (PAH), and height standard deviation score (HtSDS); (2) growth-related hormones post-treatment such as GH, IGF-1, and insulin-like growth factor binding protein-3 (IGFBP-3); (3) acceptability of the intervention measured through drop-outs that occurred during treatment for any reason; (4) drop-outs that occurred during treatment because of any adverse events; and (5) the incidence of adverse events. We included the most comprehensive report if duplicates of the same study were published in more than one journal. The detailed criteria were described in our previously published research protocol paper.[17]

2.2. Data sources and search strategy

A comprehensive literature search was carried out in the following 14 databases by one researcher (B Lee): Medline via PubMed, EMBASE from Elsevier, the Cochrane Central Register of Controlled Trials, the Allied and Complementary Medicine Database via EBSCO, the Cumulative Index to Nursing and Allied Health Literature via EBSCO, the Oriental Medicine Advanced Searching Integrated System, the Korean studies Information Service System, the Research Information Service System, the Korean Medical Database, the Korea Citation Index, the China National Knowledge Infrastructure, Wanfang data, VIP, and CiNii, from their inception up to August 4, 2020. We also searched the reference lists of included studies and relevant review articles, as well as trial registries such as Clinicaltrials.gov to identify not only the articles published in journals but also "gray literature". Furthermore, we consulted experts in pediatrics in Korean medicine to collect as much relevant literature as possible. No language restrictions were imposed. Detailed search strategies are described in Supplementary file 1.

2.3. Study selection and data extraction

Two researchers (B Lee and CY Kwon) independently conducted the study selection and data extraction process and disagreements between them were resolved through discussions with another researcher (S Jang).

Using EndNote X8 (Clarivate Analytics, Philadelphia, USA), duplicate papers found in each database and other sources were removed. The eligible literature was initially selected through a review of the title and abstract and final inclusion was determined through a full text review.

For the included studies, the following information was extracted using Excel 2016 (Microsoft, Redmond, USA): basic study characteristics (first author's name, year of publication, country, and sample size), details about the participants, interventions, comparators, and outcome measures, adverse events, and information for assessing the risk of bias of the study. We contacted the corresponding authors for the included studies via e-mail to request additional information if the data were insufficient or ambiguous.

2.4. Risk of bias assessment

Two researchers (B Lee and CY Kwon) independently assessed the risk of bias of the included studies using the Cochrane Collaboration's risk of bias 2 tool[18] and discrepancies were resolved

through discussions with another researcher (S Jang). The tool included the following items: bias arising from the randomization process, bias due to deviations from the intended interventions (effect of assignment to intervention, and effect of starting and adhering to intervention), bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. Additionally, overall bias was determined based on the results of the items. Each item was rated as "low risk," "some concerns," or "high risk."

2.5. Data analysis

For all included studies, descriptive analyses of the details of the participants, interventions, comparators, and outcomes were performed. Firstly, pairwise meta-analysis for direct comparisons was conducted using Review Manager version 5.4 software (Cochrane, London, UK) for studies that were clinically homogeneous due to using the same types of interventions, comparators, and outcome measures. Continuous variables were analyzed using the weighted mean difference (WMD) with 95% confidence interval (CI), while dichotomous variables were analyzed using the risk ratio (RR) with 95% CI. In the pairwise meta-analyses, a random-effects model was used when the heterogeneity was significant (I^2 values $\geq$ 50%), taking into account variations in trial design, although this is not a remedy for clinical heterogeneity.[19] A fixed-effects model was used when the heterogeneity was non-significant.

Afterward, we conducted a random-effect NMA based on the frequentist model, using Stata/MP software version 16 (StataCorp LLC, Texas, USA). For each outcome measure, we presented the numbers and interrelations of the interventions using a network map. After testing for clinical similarity, transitivity, and consistency, the effect size was determined through a network league table. First of all, we performed NMA for various EATM therapies by grouping them into intervention types such as HM and acupuncture. Additionally, to resolve the problem of heterogeneity caused by variations in HM evaluated in different trials, NMA was additionally performed to compare the effect size of each individual HM used when HM was used as monotherapy or add-on to GH for the primary outcome. We did not conduct NMA when there were no closed loops in the network or when few studies were included in the network, as transitivity and consistency can only be examined empirically in networks with closed loops. For the primary outcome measures, we ranked interventions based on their surface under the cumulative ranking curve (SUCRA) to identify the best treatment. However, since the comparison between control groups is out of the scope of this study, the clinical relevance is not discussed. For example, this study cannot provide reliable evidence for the comparative effect between GH and no medical treatment (two control interventions).

2.6. Quality of evidence

The quality of evidence regarding effect estimates derived for our outcomes of interest was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[20] For the direct comparison (pairwise meta-analysis), the risk of bias, indirectness, inconsistency, imprecision, and publication bias were evaluated. For the indirect comparison, we considered the lowest ratings of the two direct comparisons forming the most dominant first-order loop, and intransitivity. The higher rating of the direct or indirect estimates was determined as the quality of evidence for NMA and was presented as "high", "moderate", "low", and "very low". Furthermore, we drew conclusions considering the estimates of effect, quality of evidence, and treatment rankings (SUCRA) using the GRADE partially contextualized framework.[21]

3. Results

3.1. Study selection and study characteristics

A total of 1870 studies were found through the database search and no additional studies were identified through other sources. After removing duplicates, the title and abstract of 1695 studies were screened and 1665 studies were excluded. The full texts of the remaining 30 studies were assessed for eligibility and 14 studies[22–35] comprising 1066 participants were included in the final analysis after excluding three studies not related to ISS, five review articles, two non-RCTs, four case series, one article containing duplicate data, and one for which only the abstract was available. One of the articles[22] presented the results by age; thus, it was not included in the meta-analysis and only descriptive analysis was conducted (Fig. 1).

All of the included studies were published in China and consisted of 11 two-arm studies, two three-arm studies,[32,35] and one four-arm study.[25] A total of 10 treatment or control interventions were reported: GH, HM, acupuncture, acupressure, nutritional supplement, HM plus GH, HM plus acupuncture, HM plus acupressure, HM plus nutritional supplement, and no medical treatment. Only two articles[26,31] reported approval by the institutional review board before the start of the study, and 11 articles[23,24,26–30,32–35] stated that consent was obtained from the participants. Pattern identification was used in seven studies, of which one targeted spleen deficiency,[29] five targeted spleen or kidney deficiency,[25,26,30,32,34] and one targeted yin deficiency with effulgent fire.[35] None of the included studies reported drop-outs for any reason during the study period. The detailed study characteristics are described in Table 1.

HM was used as part of the intervention in all studies. Different HM prescriptions were used in two studies[25,30] based on pattern identification for the participants and modified basic HM prescriptions were used in two studies[22,34] according to the specific symptoms of the participants. As for the HM dosage type, decoctions were used in most of the studies, granules in five studies,[28,29,31–33] and pills in one study.[35] The duration of HM administration was over 6 months, and 6 and 12 months were the most frequent durations, with seven and six studies each. In the included studies, 55 herbs were used in total. Among them, *Poria Sclerotium* was the most commonly used (16 times), followed by *Glycyrrhizae Radix et Rhizoma* (13 times), *Atractylodis Rhizoma Alba* (13 times), *Dioscoreae Rhizoma* (11 times), *Corni Fructus* (8 times), *Citri Unshius Pericarpium* (8 times), and *Pseudostellariae Radix* (7 times) (Table 2).

NMA was only possible for the outcomes of GV per year and 6 months, 1-year post-treatment height, and bone age change after 6 months of treatment. Therefore, only pairwise meta-analysis was performed for other variables because the transitivity and consistency in the networks could not be examined. Fig. 2 shows the network map for the interventions belonging to each NMA. Nine studies[23–25,28,29,31,32,34,35] including 9 interventions (HM, GH, acupuncture, acupressure, nutritional supplement, no medical treatment, HM plus nutritional supplement, HM plus GH, and HM plus acupressure) were included in the network map of GV per year. Six studies including 6 interventions (HM, GH, nutritional supplement, no medical treatment, HM plus GH, and HM plus acupressure) were included in the network maps of GV per 6 months[23,24,26–28,31] and 1-year post-treatment height,[23,24,27–29,34] respectively. Additionally, 6 studies[23,25,26,30–32] including 6 interventions (HM, GH, acupuncture, acupressure, no medical treatment, and HM plus GH) were included in the network map of bone age change after 6 months of treatment.

Table 1
Characteristics of included studies.

Study ID	Sample size	Mean age (range) (yr)	Sex (Male:Female)	Study setting	(A) Treatment intervention	(B) Control intervention	Treatment period / F/U post-treatment	Outcome of interest reported
Bi 2015	30:30	(A) 7.3 ± 1.8 (5–11) (B) 7.4 ± 1.7 (5–11)	(A) 18:12 (B) 17:13	Department of Pediatric Endocrinology, TCM Hospital of Zhenhai District	HM + Acupuncture	Nutritional supplement (lysine, inositol, vitamin B12, and zinc for 3 mon)	6 mon / 6 mon	1. GV 2. BA change 3. IGF-1 4. IGFBP-3
Cui 2016	28:25	6–13	NR	Department of Pediatrics, Daqing TCM Hospital	HM + rhGH	rhGH 0.15–0.18 IU/kg/d	12 mon / none	1. GV 2. Height 3. BA change 4. IGF-1 5. IGFBP-3
Du 2012	49:46	Male: 6–11, female: 6–10	(A) 27:22 (B) 26:20	Growth and Development Clinic, Second Affiliated Hospital of Shandong University of TCM	HM + Acupressure	rhGH 0.12 U/kg/d	12 mon / none	1. GV 2. Height 3. BA change
Feng 2014	20:20:20:20	3–13	44:36	Growth and development clinic, Shandong Jinan Children's Hospital	(A1) HM (A2) Acupressure (A3) Acupuncture	No medical treatment	6 mon / none	1. GV 2. HtSDS 3. GV change 4. HtSDS change 5. BA change 6. peak GH 7. IGF-1
Jiang 2020	39:39	(A) 8.03 ± 1.46 (6–14) (B) 8.33 ± 1.22 (5–14)	(A) 23:16 (B) 20:19	Department of Endocrinology and Pediatrics, Shanggao People's Hospital	HM + rhGH	rhGH 0.15 IU/kg/d	6 mon / none	1. GV 2. GV change 3. BA change 4. IGF-1 5. IGFBP-3
Li 2013	35:35	Male: 6–11, female: 6–10	NR	Children's Hospital of Kaifeng City	HM + Acupressure	No medical treatment	12 mon / none	1. GV 2. Height
Sun 2017a	20:20	(A) 5.37 ± 1.22 (3.47–6.50) (B) 5.09 ± 1.54 (3.43–6.74)	(A) 13:7 (B) 9:11	Department of TCM, Zhengzhou Children's Hospital	HM	No medical treatment	12 mon / none	1. GV 2. Height 3. HtSDS 4. PAH 5. IGF-1 6. peak GH
Sun 2017b	28:28	(A) 5.54 ± 1.02 (3.33–6.67) (B) 5.35 ± 1.13 (3.0–6.83)	(A) 20:8 (B) 21:7	Zhengzhou Children's Hospital	HM	Nutritional supplement (Lysine Vitamin B12 granules, 5 g/time, bid)	12 mon / none	1. GV 2. Height 3. HtSDS 4. PAH 5. IGF-1 6. peak GH

Table 1 (continued)

Study ID	Sample size	Mean age (range) (yr)	Sex (Male:Female)	Study setting	(A) Treatment intervention	(B) Control intervention	Treatment period / F/U post-treatment	Outcome of interest reported
Tian 2017	35:45	(A) 6.50 ± 1.07 (B) 6.45 ± 1.09	(A) 20:15 (B) 25:20	(1) Department of child health or growth and development, Foshan Nanhai district maternal and child health hospital (2) Department of pediatric endocrinology, Foshan first people's hospital	HM + rhGH	rhGH 0.15 IU/kg/d	6 mon / none	1. GV 2. GV change 3. HtSDS change 4. IGF-1 change 5. IGFBP-3 change 6. BA 7. BA change
Wang 2020	20:20	(A) 7.63 ± 2.01 (4–10) (B) 7.74 ± 1.91 (5–10)	(A) 12:8 (B) 10:10	Department of Pediatrics, Fenghua District TCM Hospital	HM	No medical treatment	12 mon / none	1. GV 2. BA change 3. IGF-1 4. IGFBP-3 5. serum GH
Xu 2015	30:30:30	(A) 7.98 ± 1.89 (5–11) (B1) 8.03 ± 1.71 (6–12) (B2) 6.78 ± 1.44 (4–9)	(A) 18:12 (B1) 17:13 (B2) 16:14	Department of Pediatric Growth and Development, Jiangsu Provincial Hospital of TCM	HM	(B1) rhGH 0.15 U/kg/d (B2) No medical treatment	6 mon / none	1. GV 2. HtSDS 3. HtSDS change 4. PAH 5. PAH change 6. BA 7. BA change
Ye 2015	53:53	(A) 3.5–14 (B) 3.67–14	(A) 33:20 (B) 31:22	Department of Pediatric Growth and Development, Jiangsu Provincial Hospital of TCM	HM	HM	6 mon / none	1. GV 2. HtSDS 3. PAH change
Zhang 2017	30:30	(A) 10.26 ± 2.62 (4.8–17) (B) 10.75 ± 2.78 (6.2–14.4)	(A) 18:12 (B) 14:16	Pediatric Endocrine Clinic, Tianjin Nankai hospital	HM + rhGH	rhGH 0.15 U/kg/d	12 mon / none	1. GV 2. Height 3. IGF-1
Zhou 2012	53:53:52	(A1) 8.56 ± 0.12 (A2) 8.45 ± 0.34 (B) 8.52 ± 0.36	(A1) 0:53 (A2) 0:53 (B) 0:52	Department of Endocrinology, Zhuji Hospital of TCM	(A1) HM + Nutritional supplement (Lysine) (A2) HM	Nutritional supplement (Lysine 15 ml every night)	6 mon / none	1. GV 2. HtSDS change 3. Height 4. PAH change 5. IGF-1

Abbreviations: BA, bone age; F/U, follow up; GH, growth hormone; GV, growth velocity; HM, herbal medicine; HtSDS, height standard deviation score; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; NR, not recorded; rhGH, recombinant human growth hormone; PAH, predicted adult height; TCM, traditional Chinese medicine.

Table 2
Details of herbal medicine used in included studies.

Study ID	Name of herbal medicine	Dosage form	Administration duration	Composition and dose of individual herb (per day)	Modifying components
Bi 2015	Xiaojilipi-fang	Decoction	6 mon	Agastachis Herba 6 g, Atractylodis Rhizoma 6 g, Citri Unshius Pericarpium 6 g, Magnoliae Cortex 6 g, Galli Gigeriae Endothelium Corneum 6 g, Pseudostellariae Radix 6 g, Crataegi Fructus 10 g, Oryzae Fructus Germinatus 10 g, Poria Sclerotium 10 g, Dioscoreae Rhizoma 10 g, Picrorhizae Rhizoma 3 g	-Constipation: Trichosanthis Semen, Raphani Semen, Cistanchis Herba et al. -Diarrhea: remove Magnoliae Cortex, add Atractylodis Rhizoma Alba, Dolichoris Semen, Plantaginis Semen et al. -Yin deficiency with effulgent fire and tongue fur peeling: remove Magnoliae Cortex and Atractylodis Rhizoma, add Glehniae Radix, Trichosanthis Radix, Dendrobii Caulis et al.
Cui 2016	Pixu-tang	Decoction	12 mon	Ginseng Radix, Glycyrrhizae Radix et Rhizoma, Citri Unshius Pericarpium, Atractylodis Rhizoma Alba, Poria Sclerotium, Dioscoreae Rhizoma, Atractylodis Rhizoma, Hordei Fructus Germinatus, Epimedii Herba	–
Du 2012	Mianjian-keli	Decoction	12 mon	Poria Sclerotium 10 g, Dioscoreae Rhizoma 10 g, Atractylodis Rhizoma Alba 10 g, Pseudostellariae Radix 10 g, Citri Unshius Pericarpium 6 g, Adenophorae Radix 10 g, Polygonati Odorati Rhizoma 10 g, Lycii Fructus 10 g, Cuscutae Semen 6 g, Eucommiae Cortex 10 g, Rubi Fructus 10 g, Evodiae Fructus 10 g, Rehmanniae Radix Recens 10 g, Mori Ramulus 10 g, Zizyphi Semen 10 g, Glycyrrhizae Radix et Rhizoma 3 g	–
Feng 2014	No name	Decoction	6 mon	-Spleen-stomach weakness: Astragali Radix, Ginseng Radix, Atractylodis Rhizoma Alba, Poria Sclerotium, Liriopis seu Ophiopogonis Tuber, Crataegi Fructus, Glycyrrhizae Radix et Rhizoma -Insufficiency of kidney qi: Curculiginis Rhizoma, Epimedii Herba, Morindae Radix, Testudinis Chinemis Plastrum et Carapax, Corni Fructus, Angelicae Gigantis Radix, Glycyrrhizae Radix et Rhizoma -Dual deficiency of spleen-kidney: Astragali Radix, Ginseng Radix, Atractylodis Rhizoma Alba, Poria Sclerotium, Liriopis seu Ophiopogonis Tuber, Crataegi Fructus, Glycyrrhizae Radix et Rhizoma, Curculiginis Rhizoma, Epimedii Herba, Corni Fructus, Polygoni Multiflori Radix, Alpiniae Fructus, Glycyrrhizae Radix et Rhizoma	–
Jiang 2020	Modified Sijunzi-tang plus Bishendihuang-wan	Decoction	6 mon	Pseudostellariae Radix 10 g, Atractylodis Rhizoma Alba 10 g, Poria Sclerotium 10 g, Dioscoreae Rhizoma 10 g, Glycyrrhizae Radix et Rhizoma 3 g, Rehmanniae Radix Preparata 10 g, Corni Fructus 5 g, Eucommiae Cortex 10 g, Cervi Cornu Colla 5 g, Alismatis Rhizoma 5 g, Achyranthis Radix 5 g, Moutan Radicis Cortex 5 g	–
Li 2013	Mianjian-keli	Decoction	12 mon	Poria Sclerotium 10 g, Dioscoreae Rhizoma 10 g, Atractylodis Rhizoma Alba 10 g, Pseudostellariae Radix 10 g, Citri Unshius Pericarpium 6 g, Adenophorae Radix 10 g, Polygonati Odorati Rhizoma 10 g, Lycii Fructus 10 g, Cuscutae Semen 6 g, Eucommiae Cortex 10 g, Rubi Fructus 10 g, Evodiae Fructus 10 g, Rehmanniae Radix Recens 10 g, Mori Ramulus 10 g, Zizyphi Semen 10 g, Glycyrrhizae Radix et Rhizoma 3 g	–
Sun 2017a	Buzhongzhuchang-keli	Granule	12 mon	Ginseng Radix, Atractylodis Rhizoma Alba, Poria Sclerotium, Citri Unshius Pericarpium, Cyperi Rhizoma, Curcumae Radix, Aucklandiae Radix, Galli Gigeriae Endothelium Corneum, Massa Medicata Fermentata, Crataegi Fructus et al.	–
Sun 2017b	Buzhongzhuchang-keli	Granule	12 mon	Ginseng Radix, Atractylodis Rhizoma Alba, Poria Sclerotium, Citri Unshius Pericarpium, Cyperi Rhizoma, Curcumae Radix, Aucklandiae Radix, Galli Gigeriae Endothelium Corneum, Massa Medicata Fermentata, Crataegi Fructus et al.	–

Table 2 (continued)

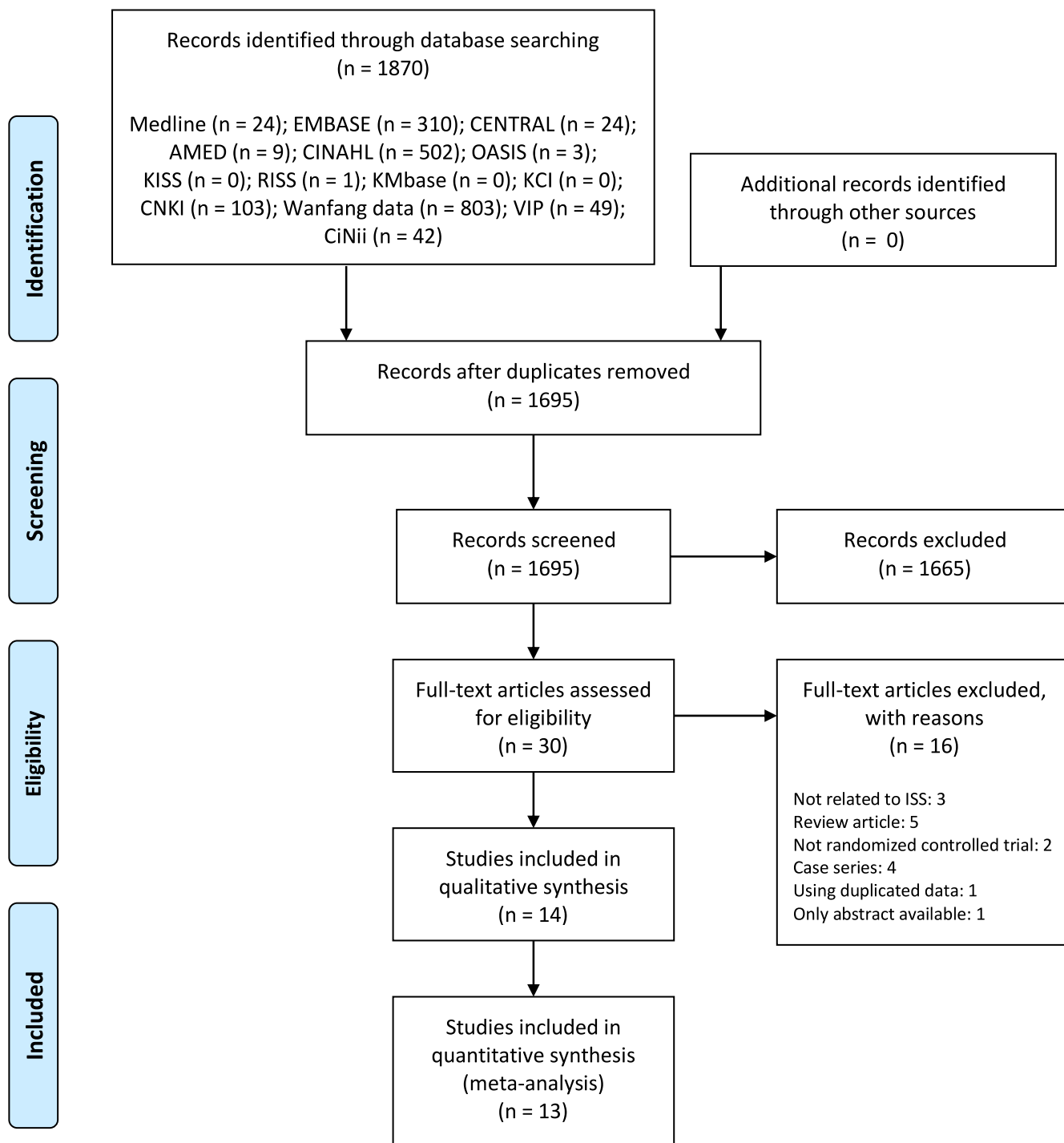| Study ID	Name of herbal medicine	Dosage form	Administration duration	Composition and dose of individual herb (per day)	Modifying components
Tian 2017	-Spleen deficiency: Modified Sijunzi-tang -Kidney deficiency: Modified Bishendihuang-wan -Dual deficiency of spleen-kidney: Modified Sijunzi-tang plus Bishendihuang-wan	Decoction	6 mon	-Spleen deficiency: Pseudostellariae Radix 10 g, Astragali Radix 10 g, Atractylodis Rhizoma Alba 10 g, Poria Sclerotium 10 g, Glycyrrhizae Radix et Rhizoma 3 g -Kidney deficiency: Cervi Cornu Colla 5 g, Dioscoreae Rhizoma 10 g, Rehmanniae Radix Preparata 10 g, Corni Fructus 5 g, Eucommiae Cortex 10 g, Achyranthis Radix 5 g, Poria Sclerotium 10 g, Moutan Radicis Cortex 5 g, Alismatis Rhizoma 5 g -Dual deficiency of spleen-kidney: Pseudostellariae Radix 10 g, Atractylodis Rhizoma Alba 10 g, Poria Sclerotium 10 g, Dioscoreae Rhizoma 10 g, Glycyrrhizae Radix et Rhizoma 3 g, Rehmanniae Radix Preparata 10 g, Corni Fructus 5 g, Eucommiae Cortex 10 g, Cervi Cornu Colla 5 g, Alismatis Rhizoma 5 g, Achyranthis Radix 5 g, Moutan Radicis Cortex 5 g	–
Wang 2020	Modified Guizhi-tang	Granule	12 mon	Dioscoreae Rhizoma 15 g, Zizyphi Fructus 10 g, Cinnamomi Ramulus 6 g, Paeoniae Radix 6 g, Corni Fructus 6 g, Zingiberis Rhizoma 3 g, Glycyrrhizae Radix et Rhizoma 3 g	–
Xu 2015	Canguizhuchang-keli	Granule	6 mon	Codonopsis Pilosulae Radix 10 g, Testudinis Chinemis Plastrum et Carapax 10 g, Astragali Radix 10 g, Atractylodis Rhizoma Alba 10 g, Poria Sclerotium 10 g, Dioscoreae Rhizoma 10 g, Eucommiae Cortex 10 g, Citri Unshius Pericarpium 6 g, Glycyrrhizae Radix et Rhizoma 3 g	–
Ye 2015	Canguizhuchang-keli	Granule	6 mon	Codonopsis Pilosulae Radix 10 g, Testudinis Chinemis Plastrum et Carapax 10 g, Astragali Radix 15 g, Atractylodis Rhizoma Alba 10 g, Poria Sclerotium 10 g, Morindae Radix 10 g	–
	Zhuangeryin oral liquid	Oral liquid	6 mon	Atractylodis Rhizoma, Crataegi Fructus, Astragali Radix, Codonopsis Pilosulae Radix, Cassiae Semen, Picrorhizae Rhizoma	–
Zhang 2017	Yishenjianpi-zhongyao	Decoction	12 mon	Pseudostellariae Radix 10 g, Astragali Radix 10 g, Atractylodis Rhizoma Alba 10 g, Dioscoreae Rhizoma 10 g, Poria Sclerotium 10 g, Rehmanniae Radix Preparata 10 g, Testudinis Chinemis Plastrum et Carapax 10 g, Cervi Cornu Colla 5 g, Corni Fructus 10 g, Psoraleae Semen 10 g, Citri Unshius Pericarpium 5 g, Alismatis Rhizoma 5 g, Glycyrrhizae Radix et Rhizoma 3 g	-Deficiency of liver blood: Lycii Fructus 10 g, Acanthopanacis Cortex 5 g, Loranthi Ramulus Et Folium 10 g -Deficiency of heart blood: Schisandrae Fructus 5 g, Polygalae Radix 10 g, Acori Graminei Rhizoma 5 g -liver depression and spleen deficiency: Bupleuri Radix 5 g, Meliae Fructus 5 g, Corydalis Tuber 5 g
Zhou 2012	Zhibaidihuang-wan plus Dabuyin-wan	Pill	6 mon	-Zhibaidihuang-wan: Anemarrhenae Rhizoma, Phellodendri Cortex, Rehmanniae Radix Preparata, Corni Fructus, Moutan Radicis Cortex, Dioscoreae Rhizoma, Poria Sclerotium, Alismatis Rhizoma -Dabuyin-wan: Rehmanniae Radix Preparata, Anemarrhenae Rhizoma, Phellodendri Cortex, Pelodiscis Carapax, Pig's spinal cord	–

Identification

Records identified through database searching
(n = 1870)

Medline (n = 24); EMBASE (n = 310); CENTRAL (n = 24);
AMED (n = 9); CINAHL (n = 502); OASIS (n = 3);
KISS (n = 0); RISS (n = 1); KMbase (n = 0); KCI (n = 0);
CNKI (n = 103); Wanfang data (n = 803); VIP (n = 49);
CiNii (n = 42)

Additional records identified
through other sources
(n = 0)

Screening

Records after duplicates removed
(n = 1695)

Records screened
(n = 1695)

Records excluded
(n = 1665)

Eligibility

Full-text articles assessed
for eligibility
(n = 30)

Full-text articles excluded,
with reasons
(n = 16)

Not related to ISS: 3
Review article: 5
Not randomized controlled trial: 2
Case series: 4
Using duplicated data: 1
Only abstract available: 1

Included

Studies included in
qualitative synthesis
(n = 14)

Studies included in
quantitative synthesis
(meta-analysis)
(n = 13)

Fig. 1. A PRISMA flow diagram of the literature screening and selection processes
AMED, Allied and Complementary Medicine Database; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; CNKI, China National Knowledge Infrastructure; ISS, Idiopathic Short Stature; KCI, Korea Citation Index; KISS, Korean Studies Information Service System; KMbase, Korean Medical Database; OASIS, Oriental Medicine Advanced Searching Integrated System; RISS, Research Information Service System.

3.2. Risk of bias assessment

None of the articles provided information on allocation concealment and none had baseline imbalances that suggested a problem with the randomization process. Therefore, all articles were judged to have some concerns in the domain of bias arising from the randomization process. In all studies, there was no information on whether participants were aware of their assigned intervention during the trial and whether there were deviations from the intended intervention beyond what would be expected in usual practice. Therefore, all articles were judged to have some concerns in the domain of bias due to deviations from intended interventions (effect of assignment to intervention). In all studies, the intervention was implemented successfully, and participants adhered to the assigned intervention regimen. Therefore, all studies were judged to have a low risk of bias in the domain of bias due to deviations from intended interventions (effect of starting and adhering to intervention). None of the studies reported outcome data
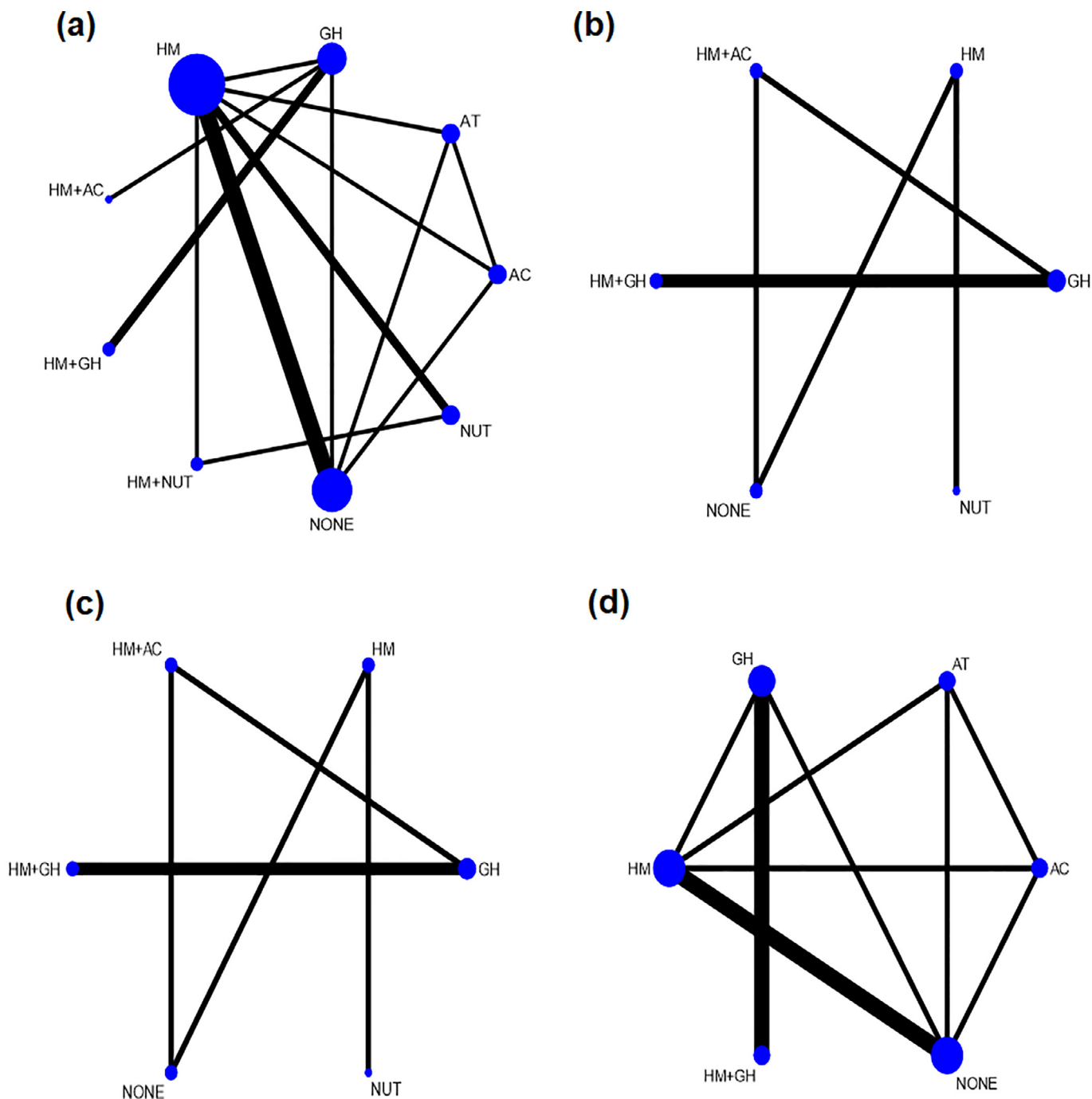
Fig. 2. Network map of (a) growth velocity per year, (b) growth velocity per 6 months, (c) height after 1 year of treatment, and (d) bone age change after 6 months of treatment

AC, acupressure; AT, acupuncture; GH, growth hormone; HM, herbal medicine; HM+AC, herbal medicine plus acupressure; HM+GH, herbal medicine plus growth hormone; HM+NUT, herbal medicine plus nutritional supplement; NONE, no medical treatment; NUT, nutritional supplement.

for all randomized participants; however, there were no missing data in all studies. Therefore, all studies were evaluated to have a low risk of bias due to missing outcome data. In all studies, there was no information on whether the intervention outcome measurement method was inadequate, whether the intervention outcome measurement method was different between the intervention groups, and whether blinding of the outcome assessor was performed. Therefore, all studies were evaluated to have some concerns in the domain of bias in the measurement of the outcome. One study[35] in which only the total effective rate was calculated without raw data was evaluated as having a high risk of bias in

the selection of the reported result. Overall, one study[35] was evaluated as having a high risk of overall bias, and the remaining studies were evaluated as having some concerns of overall bias (Fig. 3).

3.3. Meta-analysis

3.3.1. GV (pairwise meta-analysis & NMA)

The pairwise meta-analysis showed that there were no differences between HM plus GH and GH alone in GV per year (2 studies, WMD 1.19 cm, 95% CI −0.20 to 2.57, I^2=82%) and GV per 6 months (2 studies, WMD 1.15 cm, 95% CI −0.48 to 2.79, I^2=98%).

However, the change of GV per year after 6 months of treatment was significantly higher in the HM plus GH group compared to GH alone (2 studies, WMD 0.94 cm, 95% CI 0.78 to 1.09, I^2=0%). When comparing HM and no medical treatment, the GV per year (4 studies, WMD 2.35 cm, 95% CI 1.80 to 2.91, I^2=89%), GV per 6 months (1 study, WMD 1.28 cm, 95% CI 0.75 to 1.81), and change of GV per year after 6 months of treatment (1 study, WMD 1.99 cm, 95% CI 1.52 to 2.46) were all significantly improved in the HM groups. Compared to nutritional supplement, HM showed significantly better results for GV per 6 months (1 study, WMD 0.44 cm, 95% CI 0.20 to 0.68); however, there were no significant differences in GV per year (2 studies, WMD −0.08 cm, 95% CI −2.28 to 2.11, I^2=100%) (Supplementary file 2).

The results of the NMA showed that GH, HM, acupuncture, nutritional supplement, HM plus GH, HM plus acupressure, and HM plus nutritional supplement significantly increased the GV per year compared with no medical treatment. Additionally, GH increased GV per year compared to HM, acupuncture, and nutritional supplement, and HM plus GH increased it compared to HM, acupuncture, acupressure, and nutritional supplement (Table 3). In addition, GH, HM plus GH, and HM plus acupressure significantly increased the GV per 6 months compared to no medical treatment, GH compared to HM and nutritional supplement, and HM plus GH compared to HM and nutritional supplement (Table 4). Based on the SUCRA for GV per year, HM plus GH was the optimal intervention, followed by GH, HM plus acupressure, HM plus nutritional supplement, and acupuncture. Furthermore, the SUCRA for GV per 6 months of intervention showed that HM plus GH was the most favorable intervention, followed by GH, HM plus acupressure, HM, and nutritional supplement (Table 5).

We additionally performed NMA for studies using HM as monotherapy or add-on to GH for GV, our primary outcome, to compare the effect size of each individual HM used. Only a NMA of HM as monotherapy for GV per year was possible because there were no closed loops in the network, or few studies were included in the network in other outcomes. Seven studies[25,28,29,31–33,35] using a total of six types of HMs (Buzhongzhuchang-keli, Canguizhuchang-keli, Modified-Guizhi-tang, Xiaojilipi-fang, Zhibaidihuang-wan plus Dabuyin-wan, and Zhuangeryin-oral-liquid) were included in the analysis. As a result of the NMA, Zhibaidihuang-wan plus Dabuyin-wan statistically significantly improved GV per year compared to the other five HMs. Additionally, Modified-Guizhi-tang statistically significantly improved GV per year compared to the other HMs except for Zhibaidihuang-wan plus Dabuyin-wan. The Buzhongzhuchang-keli and Zhuangeryin-oral-liquid statistically significantly improved GV per year compared to Canguizhuchang-keli, and there was no significant difference between the other remaining HMs. Based on SUCRA, Zhibaidihuang-wan plus Dabuyin-wan was the optimal HM (78.7%), followed by Modified-Guizhi-tang (53.4%), Canguizhuchang-keli (48.9%), Buzhongzhuchang-keli (28.3%), Xiaojilipi-fang (17.5%), and Zhuangeryin-oral-liquid (15.2%).

3.3.2. Height (pairwise meta-analysis & NMA)

The pairwise meta-analysis showed that HM combined with GH significantly increased height after 1 year of treatment (2 studies, WMD 3.86 cm, 95% CI 2.36 to 5.36, I^2=0%) and after 6 months (1 study, WMD 4.30 cm, 95% CI 2.72 to 5.88) compared with GH alone. Moreover, HM significantly increased height after 1 year (1 study, WMD 4.07 cm, 95% CI 2.02 to 6.12) compared with no medical treatment. Compared to nutritional supplement, HM showed no significant differences in height after 1 year (1 study, WMD 0.90 cm, 95% CI −1.12 to 2.92) and after 6 months (2 studies, WMD −0.39 cm, 95% CI −3.64 to 2.86, I^2=89%) (Supplementary file 2).

The NMA results showed that HM plus GH showed statistically significant higher results in increasing 1-year post-treatment

Fig. 3. Risk of bias summary for all included studies
Low risk of bias, some concerns, and high risk of bias, respectively, are represented with the following symbols: "+", "?", and "-".

Table 3

Network league table of growth velocity per year (right upper part) and bone age change after 6 months of treatment (left lower part).

Growth hormone	−2.52 (− 4.29, − 0.75)	−2.02 (−4.41,0.37)	−3.54 (− 5.93, − 1.15)	−2.43 (− 4.65, − 0.21)	1.18 (−0.27,2.63)	−0.40 (−2.36,1.56)	−1.47 (−3.98,1.03)	−4.84 (− 6.61, − 3.07)
0.07 (−0.35,0.48)	Herbal medicine	0.50 (−1.24,2.24)	−1.02 (−2.77,0.72)	0.09 (−1.25,1.43)	3.70 (1.41,5.99)	2.12 (−0.52,4.76)	1.04 (−0.72,2.81)	−2.32 (− 3.29, − 1.35)
0.07 (−0.40,0.53)	−0.00 (−0.24,0.24)	Acupuncture	−1.52 (−3.45,0.41)	−0.41 (−2.61,1.79)	3.20 (0.40,5.99)	1.62 (−1.47,4.71)	0.55 (−1.94,3.03)	−2.82 (− 4.55, − 1.08)
0.01 (−0.46,0.47)	−0.06 (−0.30,0.18)	−0.06 (−0.32,0.20)	Acupressure	1.11 (−1.09,3.31)	4.72 (1.92,7.51)	3.14 (0.05,6.23)	2.07 (−0.42,4.55)	−1.30 (−3.04,0.44)
–	–	–	–	Nutritional supplement	3.61 (0.95,6.26)	2.03 (−0.93,4.99)	0.96 (−0.81,2.73)	−2.41 (− 4.06, − 0.75)
0.09 (−0.06,0.25)	0.03 (−0.42,0.47)	0.03 (−0.46,0.52)	0.09 (−0.40,0.58)	–	Herbal medicine + Growth hormone	−1.58 (−4.01,0.86)	−2.65 (−5.55,0.24)	−6.02 (− 8.31, − 3.72)
–	–	–	–	–	–	Herbal medicine + Acupressure	−1.07 (−4.25,2.10)	−4.44 (− 7.08, − 1.80)
–	–	–	–	–	–	–	Herbal medicine + Nutritional supplement	−3.36 (− 5.38, − 1.35)
0.01 (−0.40,0.43)	−0.06 (−0.22,0.10)	−0.05 (−0.30,0.19)	0.01 (−0.24,0.25)	–	−0.08 (−0.52,0.36)	–	–	No medical treatment

Note: Data are presented in mean difference (95% confidence interval). The result underlined meant it had statistical significant.

Table 4
Network league table of growth velocity per 6 months (right upper part) and height after 1 year of treatment (left lower part).

Growth hormone	-2.52 (-4.29,-0.75)	-2.02 (-4.41,0.37)	-3.54 (-5.93,-1.15)	-2.43 (-4.65,-0.21)	1.18 (-0.27,2.63)	-0.40 (-2.36,1.56)	-1.47 (-3.98,1.03)	-4.84 (-6.61,-3.07)
0.07 (-0.35,0.48)	Herbal medicine	0.50 (-1.24,2.24)	-1.02 (-2.77,0.72)	0.09 (-1.25,1.43)	3.70 (1.41,5.99)	2.12 (-0.52,4.76)	1.04 (-0.72,2.81)	-2.32 (-3.29,-1.35)
0.07 (-0.40,0.53)	-0.00 (-0.24,0.24)	Acupuncture	-1.52 (-3.45,0.41)	-0.41 (-2.61,1.79)	3.20 (0.40,5.99)	1.62 (-1.47,4.71)	0.55 (-1.94,3.03)	-2.82 (-4.55,-1.08)
0.01 (-0.46,0.47)	-0.06 (-0.30,0.18)	-0.06 (-0.32,0.20)	Acupressure	1.11 (-1.09,3.31)	4.72 (1.92,7.51)	3.14 (0.05,6.23)	2.07 (-0.42,4.55)	-1.30 (-3.04,0.44)
-	-	-	-	Nutritional supplement	3.61 (0.95,6.26)	2.03 (-0.93,4.99)	0.96 (-0.81,2.73)	-2.41 (-4.06,-0.75)
0.09 (-0.06,0.25)	0.03 (-0.42,0.47)	0.03 (-0.46,0.52)	0.09 (-0.40,0.58)	-	Herbal medicine + Growth hormone	-1.58 (-4.01,0.86)	-2.65 (-5.55,0.24)	-6.02 (-8.31,-3.72)
-	-	-	-	-	-	Herbal medicine + Acupressure	-1.07 (-4.25,2.10)	-4.44 (-7.08,-1.80)
-	-	-	-	-	-	-	Herbal medicine + Nutritional supplement	-3.36 (-5.38,-1.35)
0.01 (-0.40,0.43)	-0.06 (-0.22,0.10)	-0.05 (-0.30,0.19)	0.01 (-0.24,0.25)	-	-0.08 (-0.52,0.36)	-	-	No medical treatment

Note: Data are presented in mean difference (95% confidence interval). The result underlined meant it had statistical significant.

Table 5
SUCRA for interventions on each outcome.

Growth hormone	-4.32 (-8.40,-0.24)	-4.76 (-9.45,-0.07)	1.15 (-0.48,2.79)	-1.60 (-3.95,0.76)	-5.60 (-8.93,-2.27)
-17.87 (-22.79,-12.95)	Herbal medicine	-0.44 (-2.75,1.87)	5.47 (1.07,9.87)	2.72 (-0.61,6.05)	-1.28 (-3.64,1.08)
-18.77 (-24.09,-13.45)	-0.90 (-2.92,1.12)	Nutritional supplement	5.91 (0.95,10.88)	3.16 (-0.90,7.21)	-0.84 (-4.14,2.46)
3.86 (2.36,5.36)	21.73 (16.59,26.87)	22.63 (17.11,28.16)	Herbal medicine + Growth hormone	-2.75 (-5.62,0.12)	-6.75 (-10.46,-3.04)
-0.20 (-3.00,2.60)	17.67 (13.63,21.71)	18.57 (14.05,23.09)	-4.06 (-7.23,-0.89)	Herbal medicine + Acupressure	-4.00 (-6.36,-1.64)
-21.94 (-26.41,-17.47)	-4.07 (-6.12,-2.02)	-3.17 (-6.05,-0.29)	-25.80 (-30.51,-21.09)	-21.74 (-25.22,-18.25)	No medical treatment

Abbreviations: GV, growth velocity.

height compared with GH, HM, nutritional supplement, HM plus acupressure, and no medical treatment. Additionally, GH showed significantly higher results in increasing 1-year post-treatment height compared with HM and nutritional supplement, and HM plus acupressure compared with nutritional supplement and HM (Table 4).

3.3.3. PAH (pairwise meta-analysis only)

Pairwise meta-analysis showed that HM significantly increased PAH after 1 year of treatment (1 study, WMD 6.01 cm, 95% CI 3.46 to 8.56) and after 6 months (1 study, WMD 8.13 cm, 95% CI 4.45 to 11.81) compared with no medical treatment. Although there was no difference between HM and nutritional supplement after 6 months (1 study, WMD 0.26 cm, 95% CI −1.58 to 2.10), HM showed significantly higher results in PAH after 1 year, compared with nutritional supplement (1 study, WMD 4.41 cm, 95% CI 2.74 to 6.08) (Supplementary file 2).

3.3.4. HtSDS (pairwise meta-analysis only)

HtSDS was significantly changed in HM plus GH group compared to GH alone group after 6 months of treatment (1 study, WMD 0.31, 95% CI 0.22 to 0.40). Although there were no differences between HM and nutritional supplement in HtSDS after 6 months (1 study, WMD 0.03, 95% CI −0.80 to 0.86) and after 1 year (1 study, WMD 0.51, 95% CI −0.05 to 1.07), HtSDS was significantly higher in HM compared to no medical treatment after 6 months (1 study, WMD 0.26, 95% CI 0.15 to 0.36) and after 1 year (1 study, WMD 0.99, 95% CI 0.76 to 1.22) (Supplementary file 2).

3.3.5. Bone age (pairwise meta-analysis & NMA)

The pairwise meta-analysis showed that HM combined with GH significantly changed bone age after 1 year of treatment (1 study, WMD 0.40, 95% CI 0.21 to 0.59) compared with GH alone, while there was no significant difference in bone age after 6 months (1 study, WMD −0.02, 95% CI −0.48 to 0.44). Moreover, there was no significant difference in bone age change after 6 months between HM and no medical treatment (3 studies, WMD 0.05, 95% CI −0.06 to 0.16, I^2=68%) (Supplementary file 2).

The results of the NMA showed that there were no differences in change of bone age after 6 months of intervention between GH, HM, acupuncture, acupressure, HM plus GH, and no medical treatment (Table 3). The ranking analysis indicated that HM plus GH was the optimal intervention, followed by HM, acupuncture, and acupressure (Table 5).

3.3.6. Growth-related hormones (pairwise meta-analysis only)

The results of pairwise meta-analysis showed that HM plus GH showed significantly higher results compared with GH alone in IGF-1 after 6 months of treatment (1 study, WMD 83.35, 95% CI 75.81 to 90.89) and after 1 year (2 studies, WMD 61.00, 95% CI 53.36 to 68.65, I^2=0%) and in IGFBP-3 after 6 months (1 study, WMD 346.72, 95% CI 225.99 to 467.45) and after 1 year (1 study, WMD 462.20, 95% CI 314.45 to 609.95). Although there were no differences between HM and no medical treatment after 6 months in IGF-1 (1 study, WMD 42.90, 95% CI −1.70 to 87.50) and peak GH (1 study, WMD 2.02, 95% CI −1.86 to 5.90), HM showed significantly higher results after 1 year in IGF-1 (2 studies, WMD 25.59, 95% CI 17.77 to 33.41, I^2=0%), IGFBP-3 (1 study, WMD 833.93, 95% CI 799.05 to 868.81), and peak GH (1 study, WMD 3.61, 95% CI 1.65 to 5.57). There were no differences between HM and nutritional supplement in IGF-1 after 6 months (1 study, WMD −4.90, 95% CI −23.63 to 13.83) and after 1 year (1 study, WMD 15.82, 95% CI −5.66 to 37.30) and in peak GH after 6 months (1 study, WMD 0.33, 95% CI −1.29 to 1.95) and after 1 year (1 study, WMD 0.59, 95% CI −1.56 to 2.74) (Supplementary file 2).

3.3.7. Adverse events (pairwise meta-analysis only)

A total of 5 studies[23,24,28,30,32] reported adverse events during the treatment period. Pairwise meta-analysis results showed that HM plus GH or HM plus acupressure showed significantly lower adverse events rate compared with GH alone (2 studies, RR 0.13, 95% CI 0.02 to 0.97 or 1 study, RR 0.06, 95% CI 0.00 to 0.93). Cui et al[23] reported that 1 case of transient headache occurred in HM plus GH group and 2 cases of transient skin redness, 2 cases of transient headache, 1 case of obesity, and 2 cases of serum thyroxin change occurred in GH alone group. Tian and Zeng[30] re-

ported that there was no adverse event in both HM plus GH and GH alone groups. Du and Li[24] reported that there were no adverse events in HM plus acupressure group and 4 cases of mild skin redness and swelling at the injection site, 1 case of slight serum thyroxin change, and 3 cases of transient headache in GH alone group. There were no differences in incidence of adverse events between HM and nutritional supplement (1 study, RR 9.00, 95% CI 0.51 to 159.70). Sun et al[28] reported that 4 cases of dry stool were reported in HM group and there was no adverse event in nutritional supplement group. Xu[32] reported that no adverse events occurred in HM group, but did not mention whether adverse events occurred in other GH and no medical treatment groups (Supplementary file 2). All of the reported adverse events were alleviated spontaneously or after corresponding treatment.

3.4. Publication bias

Since there were no more than 10 studies in each NMA and pairwise meta-analysis, publication bias could not be evaluated using netfunnel or funnel plots.

3.5. Quality of evidence

The quality of evidence using the GRADE approach was generally "Moderate" to "Low" in both direct evidence (pairwise meta-analysis), indirect evidence, and NMA for outcomes of GV per year, GV per 6 months, height after 1 year, and bone age change after 6 months. In addition, the quality of evidence in outcome of GV per year for individual HMs as monotherapy was also mostly "Moderate". The main reason for downgrading the quality of evidence was risk of bias of the included RCTs and imprecision of the results due to wide CIs (Supplementary file 3). Based on the GRADE partially contextualized framework, when considering the effect of all the interventions on GV per year, HM plus GH might have a large beneficial effect, GH, HM plus acupressure, and HM plus nutritional supplement might have a moderate beneficial effect, and acupuncture, nutritional supplement, HM, and acupressure might have a small beneficial effect. On GV per 6 months, HM plus GH and GH alone might have a large beneficial effect, HM plus acupressure might have a moderate beneficial effect, and HM might have a small beneficial effect. On height after 1 year of treatment, HM plus GH and GH might have a large beneficial effect, and HM plus acupressure and HM alone might have a moderate beneficial effect. There might be trivial or no effect on bone age change after 6 months of treatment in all interventions, including HM plus GH, HM, acupuncture, acupressure, and GH (Supplementary file 4).

4. Discussion

4.1. Summary of evidence

In this systematic review, the authors attempted to investigate the comparative effectiveness and safety of EATM treatments for ISS using the NMA methodology. Through a comprehensive database search, 14 studies and 10 treatment or control interventions comprising GH, HM, acupuncture, acupressure, nutritional supplement, HM plus GH, HM plus acupuncture, HM plus acupressure, HM plus nutritional supplement, and no medical treatment, were evaluated.

For GV, the primary outcome in this review, most EATM treatments including HM, acupuncture, HM plus GH, HM plus acupressure, and HM plus nutritional supplement, but not acupressure alone, were associated with significant improvements compared to no medical treatment after 1 year follow-up. According to the results of SUCRA, which was used to assess the comparative effectiveness of these interventions, HM plus GH showed the most optimal effect for GV per year, GV per 6 months, and height after 1 year of treatment. In particular, this combined treatment strategy showed statistically significant improvement in 1-year post-treatment height compared to GH, HM, nutritional supplement, HM plus acupressure, and no medical treatment. NMA was not possible for the other growth-related outcomes including PAH, GV, and HtSDS, and only pairwise meta-analysis was performed for these outcomes. At 6 months and/or 1 year of treatment, HM was associated with significant improvement in all of these outcomes compared to no medical treatment. Additionally, HM plus GH showed significantly better effects on change of GV per year and HtSDS compared to GH alone after 6 months of treatment. The effects of EATM treatments on the levels of growth-related hormones such as IGF-1, IGFBP-3, and peak GH were analyzed in pairwise meta-analysis. The consistent result was that HM plus GH was significantly more effective than GH alone at improving IGF-1 and IGFBP-3 levels. Only five studies reported adverse events during the treatment period, and the pooled rate for adverse events in the HM plus GH group and HM plus acupressure group was significantly lower than that in the GH group. We additionally performed a NMA of the effect size of each individual HMs as monotherapy for GV, our primary outcome, to address the problem of heterogeneity due to variations in HM used. As a result, Zhibaidihuang-wan plus Dabuyin-wan statistically significantly improved GV per year compared to other HMs. SUCRA showed that Zhibaidihuang-wan plus Dabuyin-wan was the optimal HM for increasing GV per year, followed by Modified-Guizhi-tang and Canguizhuchang-keli.

The quality of direct and indirect evidence and NMA evaluated by the GRADE approach was usually "Moderate" or "Low". Based on the GRADE partially contextualized framework, when considering all the interventions, HM plus GH might have a large beneficial effect on GV per year, GV per 6 months, and height after 1 year of treatment without a substantial effect on change of bone age. Interestingly, EATM combination therapies such as HM plus acupressure and HM plus nutritional supplement might have moderate beneficial effects on height outcomes for children with ISS. Additionally, individual EATM therapies including acupuncture, HM, and acupressure might have a small to moderate beneficial effect on height outcome.

4.2. Strengths and limitations

This study was the first to evaluate the comparative effectiveness and safety of EATM treatments on ISS using the NMA methodology. In the context of the lack of golden-standard therapies and large medical expenditures for ISS, our findings could potentially aid in effective clinical decision-making and policy-making for ISS. However, the findings of this study should be interpreted carefully in consideration of the following limitations. First, the absolute number of included studies is small. In this review, only 14 studies involving 10 interventions were included in the analysis. For this reason, most direct and indirect comparisons were based on only 1–2 studies, which may negatively affect the reliability of the overall study results. Second, the methodological quality of the included studies was also low, and most of the studies were conducted on a small scale. This suggests that the effect size obtained in these studies may have been overestimated. In addition, most of the included studies were conducted in China, and although the risk of publication bias through funnel plots was not evaluated, the risk of potential location bias cannot be overlooked. Third, the EATM treatments used in the included studies were inconsistent. For example, among the constituents of HMs used in our analysis, frequently used herbs such as *Poria Sclerotium* or *Glycyrrhizae Radix et Rhizoma* were found, but these herbs account for only 23–29% of all HMs. This is thought to be due to the fact that the EATM approach to ISS has not yet been standardized, and rep-

resents a major challenge to be addressed in future clinical practice guidelines using expert consensus and evidence-based methodology. Fourth, as outcomes of growth, long-term follow-up over a period of several years is important. However, none of the included studies reported long-term outcomes such as adult height, and all reported only short-term growth. Fifth, sexual maturity can have a significant impact on growth outcomes. However, since the descriptions of sexual maturity in the included studies were insufficient, it is difficult for us to predict the effect of sexual maturity on the growth outcomes in these studies. Finally, we planned subgroup analysis according to the treatment period in this study's protocol,[17] but subgroup analysis was not possible due to the low number of included studies. In addition, since none of the included studies were evaluated as having a low risk of bias, sensitivity analysis to investigate the robustness of the meta-analysis results was not possible.

4.3. Suggestions for further studies

Future studies in this area can be conducted taking into consideration the following suggestions. First, the methodological quality of EATM studies on ISS needs to be further improved. For this purpose, long-term follow-up observations (e.g. adult height) of large samples though such as registry research should be conducted. In addition, even considering the characteristics of some EATMs, which make blinding of the participants and personnel difficult, it is necessary to describe appropriate random sequence generating methods and conduct the blinding of outcome assessors. Second, the heterogeneity of EATM treatments used in the included studies highlights the need for the standardization of EATM treatments for ISS. Although EATM treatments such as HM and acupuncture are individualized treatments and heterogeneity is inevitable,[36] pattern identification, a classical pathological concept in EATM, has the potential to facilitate standardization. However, evidence-based standardized pattern identification for ISS has not yet been studied and research on this is warranted. Meanwhile, from the end of 2020, evidence-based clinical practice guidelines and clinical pathways for EATM treatments for ISS are being developed with the support of health authorities in Korea and may contribute to the standardization of HM and acupuncture for ISS. Therefore, in future studies, standardization should be pursued through expert consensus and a large clinical study of ISS patients. Third, our findings suggest the potential superiority of HM plus GH, but herb-drug interaction is an important issue today,[37] and our findings do not provide a sufficient explanation for this issue. In order to encourage the combination of HM and GH in clinical practice, more preclinical and clinical evidence for herb-drug interactions should be reported. In some Asian countries where HM is already used in the national healthcare system, retrospective analysis may be attempted. Fourth, although ISS is defined as a condition in which there is no underlying medical cause for short stature, the normal growth curve for participants may affect the results of clinical studies. For example, puberty in the participants can be an important factor that results in the confusion of normal growth and growth-accelerating effects from applied interventions, potentially leading to heterogeneity between studies. Therefore, in future studies, information that can affect growth should be provided in detail in the participants' baseline data. Fifth, considering that adherence to GH in general is not high,[38] acceptability may be an important indicator of the comparative advantage of other treatments. However, through the studies included in this review, it was not possible to evaluate the acceptability data for several interventions, possibly due to insufficient reporting. In future research, the compliance and satisfaction of the participants should be evaluated, and ideally, a questionnaire for carers should be conducted. Cost-effectiveness is another important indicator for which EATM treatment may have a comparative advantage. For example, one study[39] compared the cost-effectiveness of GH with a combination EATM treatment consisting of HM, acupressure, and lifestyle modification in ISS treatment. The results demonstrated that the combined EATM treatment strategy was statistically cheaper than GH. Moreover, the increase in height was significantly higher in the EATM treatment group. In other words, better cost-effectiveness was observed for EATM. However, this study was conducted in China and is difficult to generalize to other countries. In addition, to our knowledge, studies evaluating the cost-effectiveness of other alternatives compared to GH for ISS are very rare. Therefore, it is necessary to consider this important result in future ISS intervention studies. Finally, according to a previous study,[40] minimal clinically important differences (MCID) for GV per 6 months were reported to be 0.51 cm; however, this was for children with mild short stature under the 25th percentile. Therefore, future studies on MCID calculation for GV in ISS patients will help clinicians with decision-making.

4.4. Conclusion

In this systematic review and NMA, the comparative effectiveness and safety of EATM treatments for ISS were investigated. Overall, HM plus GH showed statistically significant superiority in several growth-related anthropometric indicators compared to other EATM therapies for ISS and was associated with lower adverse events compared to GH alone. HM plus GH might have a large beneficial effect on GV per year, GV per 6 months, and height after 1 year of treatment without a substantial effect on change of bone age. However, the small number of studies included and the poor methodological quality of the studies affect the reliability of the findings. Therefore, the results of this review highlight the need for large-scale, high-quality, long-term studies that investigate the effectiveness and safety of EATM treatments for ISS.

Ethical statement

Not applicable

Data availability

The data used to support the findings of this study are included in the article.

Conflict of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2022.100832.

CRediT authorship contribution statement

Boram Lee: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Funding acquisition, Supervision. **Chan-Young Kwon:** Methodology, Writing – original draft, Writing – review & editing. **Soobin Jang:** Writing – original draft, Writing – review & editing.

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