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System Evaluation and Meta Analysis Re-evaluation of Oral Preparation of Traditional Chinese Medicine in the Treatment of Children's Hand, Foot and Mouth Disease

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Abstract: *Objective* Reevaluate the quality of literature report, methodology and evidence of systematic evaluation / meta-analysis of oral preparation of traditional Chinese medicine in the treatment of children's hand, foot and mouth disease (HFMD). *Methods* Search the systematic evaluation / meta-analysis literatures as of December 2021 from China Academic Journal Database (Wan Fang Data), China knowledge resource database (CNKI), China biomedical literature service system (SinoMed), Chinese scientific and technological journal database (VIP). Two researchers independently conduct literature screening and data extraction, and apply PRISMA statement, AMSTAR 2 tool and GRADE system to evaluate the literature quality. *Results* A total of 16 literatures were included and a number of 73 outcome indicators were included; the evaluation results of AMSTAR 2 showed that 5 were of low quality and 11 were of very low quality; GRADE showed that the evidence quality grade of one outcome index was medium, 17 were low and 55 were very low. *Conclusion* The methodological quality of systematic evaluation / meta-analysis of oral preparation of traditional Chinese medicine in the treatment of HFMD is low and very low, and the evidence quality level of outcome indicators is mostly very low. It is urgent to carry out systematic evaluation with high quality and high evidence intensity, so as to provide high-level evidence to guide clinical practice.

1. Introduction

Hand-foot-mouth disease (HFMD) is a common acute infectious disease in children, especially the preschool, caused by enteroviruses in which Coxsackievirus A16 (CV-A16) and Enterovirus 71 (EV-A71) are the most common. Most infected people are mild and a few cases can develop into severe condition with complications, even death. The incidence of the disease is high, ranging from 37.01 per 100,000 to 205.06 per 100,000 [1]. In 2018, the disease was included in The Law on the Prevention and Control of Infectious Diseases in China, Class C statutory reporting infectious diseases. Its high number of morbidity and deaths have been causing a heavy economic and

psychological burden on society and families [2].

There is currently no specific treatment for HFMD, which clinical treatment is often based on antiviral with symptomatic and supportive treatment that has certain limitations [3]. Traditional Chinese medicine has a unique advantage in antivirals and single herbs as well as compound preparations are widely used in oral treatment of HFMD [4], which the efficacy is mostly satisfactory. At present, a number of systematic reviews/meta-analyses (SR/MA) of TCM treatment of pediatric HFMD have been published. So there exist a possibility that low-quality SR/MA has the potential to be recommended as high-level evidence, which brings wrong guidance to clinical work. The re-evaluation study of SR/MA is of great significance for the determination of its quality, and also has certain significance for clinical work with the update of disease guidelines. Therefore, this paper proposes to re-evaluate the relevant SR/MA currently published, by using the PRISMA, AMSTAR 2 and GRADE evaluation systems to evaluate the quality of their reporting, methodological quality and evidence respectively, discuss and summarize the relevant outcome indicators, in order to provide more scientific decision support for clinical investigators.

2. Data and Methods

2.1 Inclusion Criteria

1) Type of study: SR/MA of HFMD treated with oral TCM medicine, and all of them are randomized controlled trials (RCTs). 2) Study subjects: The inclusion of SR/MA meets the diagnostic criteria of HFMD in Western medicine [5], gender and ethnicity are not limited, and the age < 14 years. 3) Interventions: The treatment groups are treated with oral Chinese medicine or oral Chinese medicine combined with control group, and the control groups are Western medicine or conventional treatment. 4) The outcome indicators of SR/MA include: (total) Effectiveness, time to defervescence (d), time to resolution of herpes/rash(d), time to resolution of mouth ulcers(d), time of resolution of sore throat, length of hospitalization or course of illness, time of negative viral nucleic acid, adverse reactions. 5) Language: Limited to Chinese.

2.2 Exclusion Criteria

1) SR/MA for non-RCTs, or studies doping with non-RCTs.2) The intervention is a treatment other than oral Chinese medicine. 3) Important data or content is missing that it is impossible to obtain complete data/full text of the literature. 4)Summary of meetings. 5)Mesh meta-analysis. 6)Retaining the first search version of duplicately published documents.

2.3 Retrieval Policy

Search the China Academic Journals Database (Wan Fang Data), the China National Knowledge Infrastructure (CNKI), the China Biomedical Literature Service System (SinoMed), the Chinese Science and Technology Journals Database (Weipu.com), which the SR/MA literature established until December 2021.Manually search professional materials, related journals and Internet materials. Chinese search terms: "Traditional Chinese Medicine", "Traditional Chinese Medicine", "Hand-Foot-and-Mouth Disease", "Children", "Children", "Children", "Preschool", "Random Control", "Systematic Review", "Meta-Analysis", "Meta-analysis", "Meta-analysis".

2.4 Literature Screening and Data Extraction

To use NoteExpress 3.2.0 to comb through the literature. And two investigators independently read

the title and abstract of the literature, excluding the literature that clearly does not meet the inclusion criteria, reading the full literature of possible relevance and discussing it to determine the final inclusion of the literature. Two investigators extract data on the title, author, year, overall design of the trial, sample size, participants, interventions, duration, outcome indicators, quality evaluation tools, fund support and conclusions of the included literature.

2.5 Evaluation Methods

The two researchers independently evaluate the following items. If there is any disagreement in the evaluation, make them reach an agreement through discussion.

Report quality evaluation The reported quality of the included literature is evaluated using the PRISMA statement [6]. The PRISMA consists of 27 entries, which are divided into "fully met/fully reported", "partially met/partially reported" and "not met/not reported" according to the reporting requirements of the entries.

Methodological quality evaluation The AMSTAR 2 scale tool is used to evaluate the methodological quality of the included literatures [7]. The AMSTAR 2 consists of 16 items which the evaluation results of each item are divided into yes, partial yes, and no. Among them, the key 7 entries affecting systematic evaluation are: 2, 4, 7, 9, 11, 13, 15. Based on the results of the evaluation, the quality of the systematic reviews included is divided into four levels, namely: ①high quality: there is no or only 1 non-critical entry that does not meet the requirements; ②medium quality: more than 1 non-critical entry that does not meet the requirements; ③low-quality: 1 key entry that does not meet the requirements with or without non-key items; ④Very low quality: more than 1 key entry that does not meet the requirements with or without non-key items.

Quality of evidence evaluation Grade is used to evaluate the quality of the evidence in the included literature [8]. The main principles of the evaluation include 5 factors of degradation (limitation, inconsistencies, inaccuracies, indirectness and occurrence bias) and 3 factors of escalation (amount of effect, dose response, residual confounding factors), on which the outcome indicators are classified as high-quality, medium-quality, low-quality and very low-quality based.

3. Results

3.1 Literature Screening and Process

They collected a total of 428 articles, including 112 from Wan fang data, 81 from VIP, 142 from CNKI,93 from SinoMed, getting 169 articles after removing duplicate literature through Note Express, 79 non-SR/MA articles were excluded after careful reading of the title and abstract, 30 articles' research subjects did not match, after reading the full text excluded 3 reticular meta-analysis in the rest of literature, 41 articles also were excluded because of the interference conditions for Traditional Chinese medicine were injections. Finally 16 articles were included, see Figure 1.

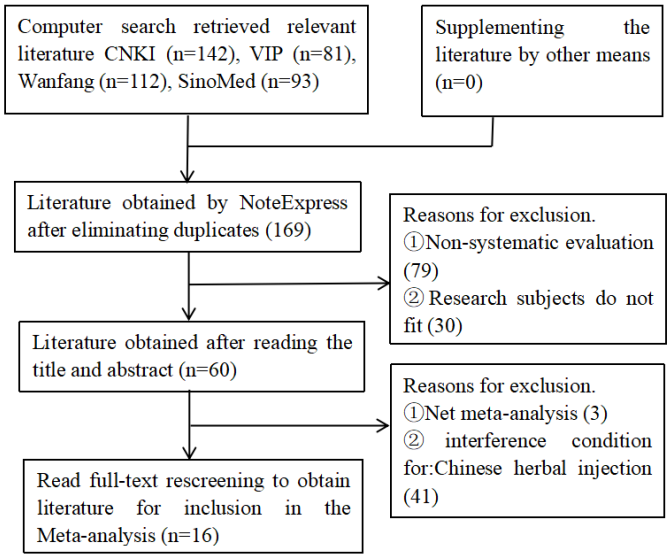

Figure 1: Literature Screening Process

3.2 Basic Features of the Included Studies

Table 1: Basic Features of 16 Studies

Researcher	Numbers	Sample Size	Whether Clear Diagnostic Criteria	Interventions		Closing Indicators	Methodological Characteristics			
				Treatment	Control		Quality Evaluation Tool	Subgroup Analysis	Sensitivity Analysis	Funnel Chart
Chen Fuchao 2011	6	594	N	①	⑩	A, B, C, D	I	N	N	Y
Huang Juan 2020	20	2182	N	①+⑩	⑩	A, B, C, D, G	II	N	N	Y
Zhou Yongkang 2014	7	1465	Y	①+⑩	⑩	A, B, C, D	II	N	Y	Y
Guo Hongju2018	6	594	Y	①+④	⑩	A, B, C, D, E, F	II	N	Y	Y
Wang Shiheng2021	63	8488	N	①/①+⑩	⑩	A, C, D, G	II	Y	N	Y
Yang Ze 2020	24	3491	Y	②+⑩	⑩	A, B, C, D, F, G	II	N	Y	Y
Chen Huihui 2020	28	3295	Y	②+⑩	⑩	A, B, C, D, F	II	N	N	Y
Shi Ning2017	9	1188	Y	③	⑩	A, B, C, D, F	II	N	Y	Y
Wu Jianting2017	8	1170	N	③/③+⑩	⑩	A, B, C, D	I	Y	N	Y
Nie Wenyi 2020	7	619	N	⑤/⑤+⑩	⑩	A, B, D, G	II	Y	N	N
Liu Liao2012	14	1792	N	⑥/⑥+⑩	⑩	A, B, C, D, F, G	II	Y	Y	Y
Dai Yanqing2017	7	966	Y	⑦/⑦+⑩	⑩	A, B, C, G	I	N	N	Y
Li Li2021	10	1461	Y	⑧+⑩	⑩	A, B, C, H	II	N	N	Y
Zhang Guoliang2014	21	2999	N	⑨	⑩	A, B, C, D	I	N	N	Y
Yu Ying2016	16	1657	N	⑨	⑩	A, B, C, F, G	II	N	N	Y
Zhang Ying2014	11	5267	Y	⑨+⑩	⑩	A, B, C	III	N	N	Y

Note: ①Pudilan Oral Liquid; ② Lanqin Oral Liquid; ③ JinLianQingRePaoTengPian; ④ Child Chiqiao Qingre Granules; ⑤ Xiao'er Chaigui Tuire Granules; ⑥ KangFuXinYe; ⑦Esberitox; ⑧ Lianhua Qingwen Capsule; ⑨Chinese herbs; ⑩ Conventional Western antiviral therapy.

A: Efficiency; B: Antipyretic time(d); C: Time of resolution of herpes/rash(d); D: Time of resolution of mouth ulcers(d); E; Time of resolution of sore throat; F: Duration or course of hospitalization; G: Adverse reactions; H: Viral nucleic acid negative time

I: Jadad; II: Cochrane; III: QUADAS

A total of 16[9-24] SR/MA were included in this study, all of which were published in Chinese journals with publication dates 2011-2021. The interventions in 4[9,16,22,23] of these articles were oral Chinese medicine alone, 12[10-15,17-21,24] were designed to be treated with oral Chinese medicine or Chinese medicine combined with Western medicine, and all literature was controlled by Western medicine interventions. In terms of methodological characteristics, 4[9,17,20,22] evaluated the quality of RCT methodology with using the Jade scale, 11[10-16,18,19,21,23] using the Cochrane bias risk assessment tool, and 1[24] using the QUADAS literature quality assessment method. Of the 16 articles, 4[13,17-19]

were subgroup analyses, 5[11,12,14,16,19] were analyzed for sensitivity, and 15[9-17,19-24] were evaluated using funnel charts to assess publication bias. See Table 1 for details.

3.3 Report Quality Evaluation of the Included Studies

Sixteen SR/MA were evaluated for report quality in accordance with the PRISMA statement, and 16 studies were fully reported with titles, structural abstracts, theoretical basis, purpose, information sources, literature screening, data extraction, bias in individual studies, generalization effect indicators, synthesis of results, study bias, intra-study bias, results of individual studies, synthesis of results, summary of evidence, limitations and outcomes.15 studies fully reported study characteristics, inter-study bias, and 8 studies reported full reporting on inclusion criteria as well as other analyses and additional analyses, 7 studies reported funding in their entirety, 16 studies partially reported searches, 15 studies partially reported on study screening, 8 studies partially reported inclusion criteria, 1 study partially reported inter-study bias, and no study fully reported protocol registration, as detailed in Table 2.

Table 2: PRISMA Results of 16 Studies

PRISMA	Full Report	Partial Reported	Not Reported
1. Title	16	0	0
2.Structured Abstract	16	0	0
3.Theoretical basis	16	0	0
4.Purpose	16	0	0
5.Program Registration	0	0	16
6.Inclusion Criteria	8	8	0
7.Information Sources	16	0	0
8.Search	0	16	0
9.Literature Research Screening	16	0	0
10.Information Extraction	16	0	0
11.Data entry	16	0	0
12.Individual Study Bias	16	0	0
13.Generalized Effect Indicators	16	0	0
14.Synthesis of Results	16	0	0
15.Study Bias	16	0	0
16.Other Analysis	8	0	8
17.Study Screening	0	15	1
18.Study Characteristics	15	0	1
19.Study Internal Bias	16	0	0
20.Results of Individual Studies	16	0	0
21.Synthesis of Results	16	0	0
22.Inter-study Bias	15	1	0
23.Additional Analysis	8	0	8
24.Summary of Evidence	16	0	0
25.Limitations	16	0	0
26.Endpoints	16	0	0
27.Funding	7	0	9

3.4 Methodological Quality Assessment of Included Studies

The methodological quality of the studies included in the literature was evaluated according to the AMSTAR 2 score entries (table), including 0 high and medium confidence studies, 5 low confidence studies (31.25%), and 11 very low confidence studies (68.75%), as detailed in Table 3

Table 3: AMSTAR 2 for 16 Studies

Researcher	AMSTAR2																Overall Quality
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
ChenFuchao 2011	+	-	+	±	-	+	±	±	+	-	+	+	+	-	+	-	EL
Huang Juan 2020	+	-	+	±	+	+	±	±	+	-	+	+	+	-	+	-	EL
ZhouYongkang 2014	+	-	+	±	-	-	-	±	+	-	+	+	+	-	+	-	EL
Guo Hongju2018	+	-	+	±	+	+	±	±	+	-	+	+	+	-	+	-	EL
WangShiheng2021	+	-	+	±	+	+	+	±	+	-	+	+	+	-	+	-	L
Yang Ze 2020	+	-	+	±	+	+	+	±	+	-	+	+	+	-	+	-	L
Chen Huihui 2020	+	-	+	±	-	+	±	±	+	-	+	+	+	-	+	-	EL
Shi Ning2017	+	-	+	±	+	-	±	±	+	-	+	+	+	-	+	-	EL
WuJianting2017	+	-	+	±	+	+	+	±	+	-	+	+	+	-	+	-	EL
Nie Wenyi 2020	+	-	+	±	+	+	+	±	+	-	+	+	+	+	-	-	L
Liu Liao2012	+	-	+	±	-	+	±	±	+	-	+	+	+	-	+	-	EL
Dai Yanqing2017	+	-	+	±	+	-	-	±	+	-	+	+	+	-	-	-	EL
Li Li2021	+	-	+	±	-	+	±	±	+	-	+	+	+	-	+	-	EL
Zhang Guoliang2014	+	-	+	±	+	+	-	±	+	-	+	+	+	-	+	-	L
Yu Ying2016	+	-	+	±	+	+	+	±	+	-	+	+	+	-	+	-	L
Zhang Ying2014	+	-	+	±	-	+	-	±	+	-	+	+	+	-	+	-	EL

Note: “+”, “±”, “-”represent“ Compliant ”, “Partially Compliant”, “Not Compliant”
EL= Extremely Low; L=Low.

3.5 Quality of the Evidence for the Included Studies

The quality of the evidence generated in the included studies was evaluated according to the GRADE system, involving a total of 73 outcome measures, of which 55 were of very low quality (75.3%), 17 were of low quality (23.3%), 1 was of medium quality (1.3%), and 0 were of high quality. In the longitudinal analysis of the downgrade factors, limitations (moderate bias in one or more RCTs included), publication bias (funnel asymmetry or small but positive sample sizes in the included studies) and inconsistencies (large heterogeneity) were the main factors contributing to the reduction in the quality of the evidence, and inaccuracies (small sample size, 95% CI confidence interval width) also had an impact on the quality of the evidence, all the evidence bodies did not meet the criteria for upgrading. See Table 4 for details.

Table 4: GRADE for 16 Studies

RESEARCHER	Conclusion Indicators	Downgrading Factors					Upgrade Factors			Evidence Quality
		Limitation	Inconsistency	Non-directivity	Inaccuracy	Publication Bias	Amount of Effect	Dose Response	Residual Confounding Factors	
Chen Fuchao2011	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
Huangjuan2020	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Adverse reactions	-1	0	0	-1	-1	0	0	0	EL
Zhou Yongkang2014	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL

	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
Guo Hongju2018	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of sore throat	-1	-1	0	0	-1	0	0	0	EL
	Duration or course of hospitalization	-1	-1	0	0	-1	0	0	0	EL
Wang Shiheng 2021	Efficiency	-1	0	0	0	-1	0	0	0	L
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Adverse reactions	-1	0	0	-1	-1	0	0	0	EL
Yangze2020	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	0	0	0	-1	0	0	0	L
	Time of resolution of herpes/rash	-1	0	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Duration or course of hospitalization	-1	-1	0	0	-1	0	0	0	L
	Adverse reactions	-1	0	0	-1	-1	0	0	0	EL
Chen Huihui2020	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Duration or course of hospitalization	-1	-1	0	0	-1	0	0	0	EL
Shining2017	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Duration or course of hospitalization	-1	-1	0	0	-1	0	0	0	EL
Wu Jianting2017	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
Nie Wenyi2020	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Adverse reactions	-1	0	0	-1	-1	0	0	0	EL
Liuliao2012	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
	Duration or course of hospitalization	-1	-1	0	0	-1	0	0	0	EL
	Adverse reactions	-1	0	0	-1	-1	0	0	0	EL
Dai Yanqing2017	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Adverse reactions	-1	0	0	-1	-1	0	0	0	EL
Lili2021	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Viral nucleic acid negative time	0	0	0	0	-1	0	0	0	中

Zhang Guoliang2014	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of mouth ulcers	-1	-1	0	0	-1	0	0	0	EL
Yuying2016	Efficiency	-1	0	0	0	-1	0	0	0	L
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL
	Duration or course of hospitalization	-1	-1	0	0	-1	0	0	0	EL
	Adverse reactions	-1	0	0	-1	-1	0	0	0	EL
Zhangying2014	Efficiency	-1	-1	0	0	-1	0	0	0	EL
	Antipyretic time	-1	-1	0	0	-1	0	0	0	EL
	Time of resolution of herpes/rash	-1	-1	0	0	-1	0	0	0	EL

Note: “-1”, “0”, “+1”represent “Downgrade one level”, “Unchanged level”, “upgrade one level” EL= Extremely Low; L=Low.

3.5.1 Total Efficiency

Sixteen [9-24] articles focused on clinical (overall) effectiveness, of which 1 was of very low quality evidence[24] and the remaining 15 were of low quality, of which 3 [9,11,24] focused on clinical recovery rates, all showing that the cure rate of HFMD in the treatment of Traditional Chinese medicine or Chinese medicine in combination with Western medicine was higher than that of the Western medicine group alone, of which 4 [9,16,22,23] were compared with Western medicine alone, all showing that the experimental group was more efficient than the control group, and 11 [10-15,17-18,20-21,24] were oral therapy of traditional Chinese medicine or combination of traditional Chinese medicine and Western medicine, which show that traditional Chinese medicine or combination of traditional Chinese medicine and Western medicine is superior to Western medicine alone. 1 article [18] showed that the effective rate of Xiao′er Chaigui Tuire Granules combined with Creatine phosphate disodium salt was not significantly different from that of Creatine phosphate disodium salt alone. The quality of evidence was extremely low.

3.5.2 Antipyretic Time

Fifteen [9-12,14-24] articles concerned about the antipyretic time, of which 4 [9,16,22,23] analyzed the treatment of Chinese medicine alone compared with Western medicine treatment, showing that the Chinese medicine group can significantly shorten the antipyretic time, which the quality of the evidence was extremely low. 11 of them used the loading design [10-12,14,15,17-21,24], showing that the use of Chinese medicine alone or in combination with Western medicine can significantly shorten the antipyretic time, which the quality of evidence in one of them was low [14]. The remaining 10 pieces of evidence were of very low quality[10-12,15,17-21,24].

3.5.3 Time of Resolution of Herpes/Rash

Fifteen articles [9-17,19-24] focused on herpes/rash resolution time, four of which [9,16,22,23] were treated with Chinese medicine alone, showing that TCM treatment shortened the time for herpes/rash resolution, which the quality of evidence was very low, of which 11[10-12,13,15,17-21,24] were loaded and showed that TCM treatment or combined with Western medicine therapy shortened the time for herpes/rash resolution, which the quality of the evidence was extremely low.

3.5.4 Time of Resolution of Mouth Ulcers

Twelve [9-19,22] articles were concerned about the time of resolution of mouth ulcers, of which 3 [9,16,22] were treated with oral Chinese medicine alone, which the quality of the evidence was very low. Of which 9 [10-15, 17-19] were loaded design, showing that traditional Chinese medicine or combination of traditional Chinese medicine and Western medicine can shorten the time of oral ulcer resolution, which the quality of evidence was very low.

3.5.5 Time of Resolution of Sore Throat

Only one article [12] focused on the time of sore throat resolution, with the combination of two proprietary Chinese medicines, showing that the combination of two proprietary Chinese medicines can shorten the resolution time of sore throat, which the quality of the evidence was extremely low.

3.5.6 Duration or Course of Hospitalization

Six [12,14-16,19,23] articles focused on duration or course of hospitalization, of which 2 [16,23] showed that Chinese medicine alone shortened the duration or course of hospitalization, which the quality of evidence was very low. Four [12,14,15,19] articles showed that traditional Chinese medicine treatment or combination with Western medicine therapy significantly shortened duration or course of hospitalization. One [14] of the quality of evidence was low, the quality of evidence in the remaining 3[12,15,19] was very low.

3.5.7 Viral Nucleic Acid NegativeTime

Only one article[21] focused on the time of viral nucleic acid negative, which used the combination of Chinese and Western drugs, showing that the combination of Chinese and western drugs can shorten the time of viral nucleic acid negative, which the quality of evidence is medium.

3.5.8 Adverse Reactions

Seven[10,12-14,18,20,23] articles were concerned about adverse reactions, of which 1[23] was treated with Chinese medicine alone, showing that the adverse reactions caused by Chinese medicine alone were less than in the control group, which the quality of the evidence was very low.6[10,12-14,18,20] articles were traditional Chinese medicine or combination of traditional Chinese and Western medicines, of which 2[10,14] showed no difference between the adverse reactions of the experimental group and the control group, which the quality of the evidence was extremely low. There were 3[12,18,20] articles not clearing adverse reactions due to the small sample size, non-comparison and so on. 1 article[13] analyzed that Ribavirin is safer than Pudilan Oral Liquid, and Pudilan Oral Liquid is safer than conventional treatment.

4. Discussion

Of the 16 SR/MA included in this study, the results of the AMSTAR 2 methodological quality evaluation showed that 11 studies were of very low quality and 5 studies were of low quality with no medium or high quality studies. The main problems include: (1) None of the 16 studies have developed a preliminary research protocol and registration, which may increase the risk of bias in the study to a certain extent. AMSTAR 2 requires a systematic evaluation to indicate whether to develop a preliminary research protocol and register, meanwhile, to describe in detail the inconsistencies with the previous research protocol in the actual research process. (2) The articles included in this paper was searched in more detail, but no systematic literature search format was provided, 6 studies did not use double repetitive literature screening, which items that were not systematically searched may result in incomplete or inaccurate literature searches, affecting the final evaluation results. Three studies did not use two-person duplicate data extraction, which may result in some extracts being missing or incorrect. (3) Four studies did not provide reasons and lists of excluded literature and 7 studies only provided partial reasons and lists of excluded literature, which did not ensure the transparency of literature screening. It is pointed out that investigators should provide a list of excluded literature and exclusion reasons in detail (e.g., in the format of tables or references) when conducting systematic reviews in AMSTAR 2. (4) All 16 studies did not adequately describe the basic characteristics of the included literature. (5) None of the 16 studies reported on the source of research

funding, nor did they report on potential sources of conflicts of interest, which may lead to doubt about the authenticity of the findings and the influence of interest groups on the findings. (6) Fifteen studies assessed the risk of bias in the included studies through funnel charts, but the causes of bias were not explored in depth. (7) Eight studies did not explore heterogeneity between studies and seven studies attempted to explain the sources of heterogeneity through subgroup analysis or sensitivity analysis, but the explanation and discussion were not satisfactory. The influencing factors associated with high heterogeneity were not analyzed in depth, resulting in a decrease in the statistical credibility of meta-analysis.

The results of the quality assessment of the included studies show that there is a serious lack of reporting information mainly in the following aspects: (1) None of them mention the registration of the program with the lack of awareness of the formulation of the program and registration. (2) Eight articles reported inclusion criteria, while other studies did not elaborate on inclusion criteria, which may cause inconsistencies in the baseline of cases and bias. (3) No study fully reported retrieval, which may lead to incomplete retrieval. (4) The evidence summary is not comprehensive enough, and a comprehensive analysis of the relevance to major interest groups is lacking. (5) Lack of funding sources and descriptions of conflicts of interest, the reader cannot judge whether there is an impact of interest on the results of the study.

Grade quality of the evidence was graded on 73 outcome measures in 16 articles, which there were no measures of high evidence quality, only one (1.4%) moderate-quality outcome measure, low-quality outcome measures of 23.3%, and very low-quality outcome measures of 75.3%. There were no escalating factors in outcome measures in 16 studies, with both limitations and publication bias were reduced by one level. The vast majority of outcome measures were downgraded one level in inconsistencies, mainly due to the high heterogeneity. The reference standards for relevant indicators were not mentioned in the original study and there is no uniform standard, which will reduce the credibility of the strength of the evidence to a certain extent. The results of this study show that the SR/MA of oral Chinese medicine for the treatment of pediatric HFMD should be based on the Amstar2 and PRISMA in terms of methodology and literature information reporting, especially before the study. A detailed implementation plan should be formulated and implemented in accordance with the research plan, the actual study process and the program should be recorded in detail to control the risk of bias. The effect of the bias risk of individual studies on SR/MA results should be evaluated, as well as the reasons and list of exclusion literature should be provided. The risk of bias in the included studies should be fully assessed, potential conflicts of interest reported, etc. The reason for the low strength of Grade evidence is mainly due to the low quality of the original study literature and the methodological quality of the systematic review. Therefore, in the future, researchers who conduct clinical trials such as oral Chinese medicine for the treatment of pediatric HFMD should specify a reasonable scheme when conducting the original study, standardize randomization, allocation, blinding, etc. To improve the quality of the original study, reduce the risk of bias, select appropriate outcome indicators, and pay attention to the organic combination of TCM syndrome typing and Western medicine indicators, refer to the STOC controlled trial guidelines for methodological design[25]. At the same time, researchers should also make plans in advance when performing SR/MA and register on relevant platforms[26, 27], standardize and improve the quality of methodological and literature reports, in order to provide a higher quality basis for oral Chinese medicine treatment of pediatric HFMD.

The following limitations exist in this study: (1) the included literatures are only Chinese' and the other language literatures and grey literatures are not searched, which may cause some data may missing; (2) the interventions and control measures of all the included studies are not exactly the same, which may lead to higher heterogeneity of the studies, thereby reducing the level of evidence; (3) the quality evaluation using the AMSTAR 2, PRISMA and GRADE is highly subjective and has

a certain impact on the evaluation results.

The available evidence suggests that the methodological quality of SR/MA for the treatment of pediatric HFMD by oral Chinese medicine is extremely low. The quality of reports is also insufficient and the quality of evidence is also low. The recommendation and clinical application of relevant guidelines are cautious. At the same time, relevant investigators should standardize the process when conducting clinical trials and SR/MA and raise the threshold for inclusion in SR/MA studies to obtain higher quality research evidence and provide a higher quality basis for oral Chinese medicine treatment of pediatric HFMD.

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