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Review Article

Compound glycyrrhizin injection for improving liver function in children with acute icteric hepatitis: A systematic review and meta-analysis

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ABSTRACT

Background: Compound glycyrrhizin injection (CGI) is a preparation with glycyrrhizin as the main active ingredient extracted from licorice. As clinical trials suggest that CGI is effective in improving liver function for acute icteric hepatitis in children (AIHC), this systematic review aimed to evaluate and verify its therapeutic effects and safety.

Methods: Six electronic databases were searched from their inception to 15 May 2021. Randomized controlled trials (RCTs) assessing therapeutic effects and safety of CGI for AIHC were included. The risk of bias for each trial was assessed using the Cochrane Risk of Bias Tool 2.0. Primary outcomes were indexes related to liver function, including total bilirubin (TBiL), alanine aminotransferase (ALT) and aspartate transaminase (AST). RevMan 5.4 software was used for data analyses. The certainty of the evidence was assessed using the online GRADEpro tool.

Results: Six RCTs involving 608 children were included. The overall bias was assessed as having "high risk of bias" in all trials. All trials compared the combination of CGI and conventional western medicine (CWM) with CWM alone. Regarding the effects of CGI for AIHC, results showed that CGI plus CWM was superior to CWM alone in reducing the levels of TBiL (mean difference (MD) = -8.19 mmol/L, 95% CI -9.86 to -6.53), ALT (MD = -24.09 U/L, 95% CI -30.83 to -17.34) and AST (MD = -18.67 U/L, 95% CI -21.88 to -15.45). No trial reported adverse events. The certainty of the evidence for outcomes were all evaluated as low or very low.

Conclusion: CGI may have adjuvant therapeutic effects on improving the liver function of children with AIHC. There is no evidence to determine the safety of CGI for AIHC. As current evidence is weak, further well-designed RCTs are required for verification of the therapeutic effects of CGI.

1. Introduction

Acute icteric hepatitis (AIH) is one of the clinical sub-types of acute hepatitis caused by hepatitis A, B, C, D and/or E virus, with adverse changes in bilirubin as the main characteristic[1–3]. AIH develops rapidly and is highly infectious. Children are easily affected by hepatitis virus infection resulting in various adverse effects such as imperfect organ development and a poor immune system function. This can lead to the occurrence of hepatitis such as acute icteric hepatitis in children (AIHC). AIHC may lead to a variety of conditions (such as hepatic ascites, cirrhosis), if this cannot be resolved in a timely manner it can seriously affect a child's health and life[4]. The main clinical symptoms of this disease include fever, hepatomegaly, and pain in the liver area. Liver function examination has shown that the levels of total bilirubin (TBiL), alanine aminotransferase (ALT) and aspartate transaminase (AST) are significantly increased.

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In clinical practice, commonly used medications for the treatment of AIH include interferon, ribavirin, glutathione, etc. However, the effectiveness of these medications is often poor.[5] Compound glycyrrhizin injection (CGI) is a colorless clear liquid prepared with glycyrrhizin as the main active ingredient, with glycine and cysteine hydrochloride as additional ingredients. Glycyrrhizin as a compound, is an active ingredient extracted from Gan Cao (*Glycyrrhiza uralensis Fisch. ex DC.*), has been reported to have various important biological activities,[6] such as anti-oxidant properties, anti-cancer properties and anti-inflammatory action.[7–9] The preparation is registered in China and produced by many different companies. In Japan, glycyrrhizin injections have been used as a therapeutic drug for allergy inflammation since 1948 and for chronic hepatitis since 1979.[10] By acting on multiple targets in inflammatory pathways such as phospholipase A2 and high mobility group protein 1,[11,12] glycyrrhizin can inhibit the inflammatory response, reduce the pathological damage of the liver and repair damaged liver cell function[13,14]. Additionally, glycyrrhizin belongs to a biological macromolecule with strong polarity, so the bioavailability of injection is higher than that of oral administration.

Currently, many randomized controlled trials (RCTs) on CGI for AIHC have been conducted. However, we were unable to find any systematic reviews on CGI for the treatment of AIHC, which could provide a high level of evidence to justify clinical practice. In order to further evaluate and verify the therapeutic effects and safety of CGI for children with AIHC in improving their liver function and to provide better evidence for clinical practice, a systematic review and meta-analysis was conducted.

2. Methods

2.1. Inclusion and exclusion criteria

2.1.1. Inclusion criteria

Inclusion criteria followed the **PICOST** (Participants, Interventions, Comparators, Outcomes, Study design, Time periods) framework, 1) Participants: Children diagnosed as AICH and infected with one or two or more of hepatitis A, B, C, D and E viruses. Age was younger than or equal to 14 years old, but no restrictions on gender or race. 2) Interventions: This could be CGI, or CGI combined with the comparator. 3) Comparators: These could be either conventional western medicine (CWM), placebo or no treatment. 4) Outcomes: Primary outcomes were indexes related to liver function, including total bilirubin (TBiL), alanine aminotransferase (ALT) and aspartate transaminase (AST).[15,16] Secondary outcomes included global improvement of symptoms, the disappearance rate and duration of icterus, adverse events. For the global improvement of symptoms, these were classified into two levels: effective and ineffective. If the clinical symptoms (vomiting, fever, nausea, etc) did not improve or even deteriorated compared with before treatment, this was recorded as ineffective. Otherwise they would be called effective. The effective rate = (number of effective participants / total number of participants) × 100%. 5) Study design: Only RCT(s) were included. 6) Time periods: All lengths of treatment time and duration of follow-up were eligible. For outcomes reported at multiple time points, we used the longest reported follow-up time point.

2.1.2. Exclusion criteria

1) The full text of articles could not be obtained; 2) any duplicated articles; 3) Clinical trial protocols.

2.2. Retrieval platforms and search strategies

PubMed, Web of Science, SinoMed, China National Knowledge Infrastructure (CNKI), Wanfang Database, the China Science Technology Journal Database (VIP) were searched from their inception to August 15, 2020. The search terms include Fu Fang Gan Cao Suan Gan, Fu Fang Gan Cao Tian Su, Mei Neng, Pai Gan Neng, Gan Yan, Huang Dan, Compound Glycyrrhizin, Hepatitis, Icteric and Icterus. Search strategies for all the electronic databases can be found in Supplement-Appendix 1.

We updated the search and selected the latest published trials that met the inclusion criteria, as to May 15, 2021.

2.3. Trial selection and data extraction

Trials were selected according to the inclusion/exclusion criteria by reading the titles, abstracts and (or) full texts of the published articles.

Two authors extracted the data independently from the included trials using a pre-designed data extraction sheet, evaluated and cross-checked. The entries of extraction include article titles, authors' information, characteristics of participants (sample size, age and disease severity, etc), details of interventions and comparators, outcomes, information relevant to trial design, etc. Any disagreements were resolved by discussions with a third author (JPL).

2.4. Risk of bias

The risk of bias of each included trial was evaluated using the Cochrane risk of bias tool 2.0[17] by two authors independently. The inconsistencies were discussed with the third author (JPL). The tool consists of the following five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Each domain was judged as low risk of bias, high risk of bias, or some concerns.

2.5. Data synthesis

The data were synthesized descriptively, including summary statistics and detailed tables of trial characteristics.

With regard to the outcomes of CGI for AIHC, the data was pooled by conducting meta-analysis, if data allowed, by using Review Manager 5.4 (Revman 5.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) software. We presented binary data as a risk ratio (RR) with its 95% confidence interval (CI), and continuous data as a mean difference (MD) with its 95% CI. The random-effects model was used for meta-analysis considering potential sources of clinical heterogeneity. If $P < 0.10$, this indicated that there was heterogeneity among the included trials. Meanwhile, we also referred to the value of I^2. The smaller the value of I^2, the smaller the statistical heterogeneity.[18] When $P < 0.10$ and $I^2 > 50\%$, the accuracy of the data was checked first. If the data was accurate, subgroup analysis based on children' baseline, interventions and comparators and/or sensitivity analysis based on methodological quality would be conducted, if appropriate, to explore the source of heterogeneity. Otherwise, we would interpret the result carefully.

The following subgroup analyses would be conducted, according to the protocol, if appropriate: 1) Subgroup analysis based on the severity of AIHC, to detect whether the seriousness of AIHC has an impact on the effects; 2) Subgroup analysis based on the different courses of treatment, to see whether children can benefit more from long-term treatment; 3) Subgroup analysis based on medication dosage of CGI, to explore whether children can get more benefit from a high dosage.

Although planned, we did not construct funnel plots to evaluate publication bias as these are inaccurate when fewer than 10 trials are included in the analysis.[19] In addition, the certainty of

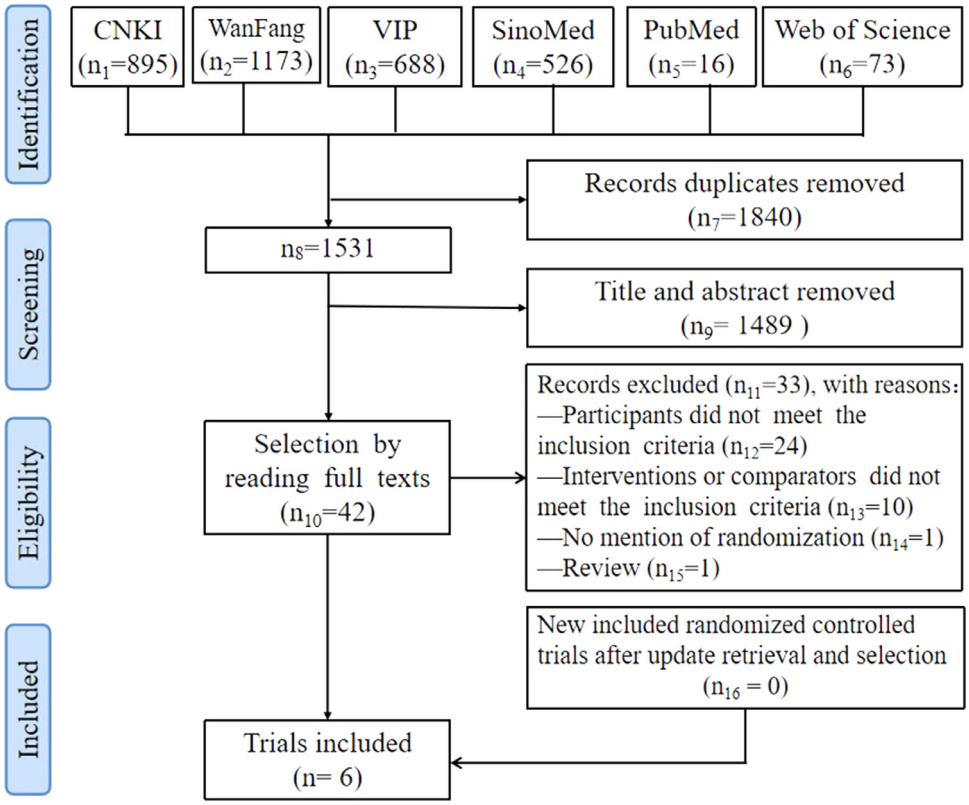

Fig. 1. Flow diagram of search and literature selection.

the evidence for each outcome was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation criteria) approach[20] to conduct management recommendations by the GRADEpro Guideline Development Tool (GDT) online (https://gradepro.org/).

3. Results

3.1. Literature search and selection

A total of 3371 records were identified by searching electronic databases. We excluded 1840 duplicate records, and 1489 records were excluded by screening the titles and abstracts. The remaining 42 records were selected by screening full-texts, and 36 were removed for various reasons (see Fig. 1). No new randomized controlled trial was included after an updated retrieval and selection, up to May 15, 2021.

Finally, six articles (representing six individual trials[21–26]) were included in this review. Fig. 1 provides the flow diagram on the search and screening of trials.

3.2. Characteristics of included trials

Six two-armed RCTs[21–26] involving 608 participants were included in this review, all were published in Chinese. The age range of participants was 2-12 years old according to four trials[21,24–26], and the ratio of boys to girls was 1.2: 1. Four trials[21–23,26] reported the types of hepatitis of the participants and the number of participants corresponding to each type of hepatitis. Participants in each of these four trials[21–23,26] involved viral hepatitis type A, viral hepatitis type B and mixed hepatitis. Only one trial[26] reported the severity of icterus, including 66 mild, 25 moderate and 3 serious cases. In all trials, the intervention was CGI plus comparator and the administration of CGI was an intravenous drip. The children in the comparator group were treated with CWM (potassium magnesium aspartate, creatinine, vitamin C and/or an energy mixture, etc). The treatment course of included trials was either 14 or 15 days duration.

The characteristics of all the included trials are summarized in Table 1.

3.3. Assessment of risk of bias

The risk of bias summary and graph of included trials is given in Fig. 2.

a) *Domain 1: Risk of bias arising from the randomization process*

For random sequence generation, one trial[25] used the method of random number tables, one trials[24] used lot-drawing, and the other four trials[21–23,26] only mentioned “random” or “randomization” without describing their methods in detail. For allocation concealment, no trial reported relevant information. If allocation concealment was not implemented, there is reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation. Therefore, this domain for all the[21–26] included trials was judged as “some concerns” due to insufficient information.

a) *Domain 2: Risk of bias due to deviations from the intended interventions*

Although one[25] trial reported using a double-blind design and the other five trials[21–24,26] did not report blinding information, judged in the light of the interventions and comparators, it was impossible to blind the clinicians implementing treatments. Taking the above into consideration, deviations from the intended interventions may exist. However, all trials[21–26] did not report relevant

Table 1
Characteristics of the included studies.

ID	Sample size (M/F)		Age (years)		Type of hepatitis (No. of participants for each type)		Severity of disease		Intervention		Course of treatment (days)	Outcomes
	T	C	T	C	T	C	T	C	T	C		
Huang LL2016[21]	36/24	34/26	6.9±2.4 (4-11)	6.7±2.1 (5-12)	A(39); B(15); Mixed(6)	A(40); B(15); Mixed(5)	Not reported		60-80ml Compound glycyrrhizin injection dissolving in 250ml 5% glucose solution, ivgtt qd (+ Comparator)	Conventional western medicine (30ml PMA dissolving in 250ml 5% glucose solution, ivgtt qd; 0.2g creatinine, 20g vitC, 150ml energy mixture qd)	15	①②④
Wang WF2015[22]	27/21	26/22	4.5±1.4	4.4±1.6	A(16); B(26); Mixed(6)	A(17); B(26); Mixed(5)	Not reported		10-60ml Compound glycyrrhizin injection, ivgtt qd (+ Comparator)	Conventional western medicine (5-20ml PMA, ivgtt; creatinine, vitC, energy mixture, etc)	14	①②③④
Liu JL2015[23]	22/20	24/18	4.7±1.6	4.9±1.8	A(16); B(22); Mixed(4)	A(14); B(23); Mixed(5)	Not reported		50ml Compound glycyrrhizin injection ivgtt qd (+ comparator)	Conventional western medicine (25ml PMA, ivgtt qd; creatinine, vitC, energy mixture, etc)	14	①②③④
Yang M2020[25]	14/12	13/13	6.2±1.3 (3-9)	5.7±1.2 (2-8)	Not reported		Not reported		60ml Compound glycyrrhizin injection dissolving in 250ml 5% glucose solution, ivgtt qd (+ comparator)	Conventional western medicine (PMA, creatinine, vit)	14	①②③④
Chen QJ2016[26]	42/39	41/40	2-7	3-7	Not reported		Not reported		20ml Compound glycyrrhizin injection, ivgtt qd (+ comparator)	Conventional western medicine (1g PMA, ivgtt qd; 0.2g creatinine and 2g vitC dissolving in 5% glucose solution, ivgtt qd)	14	④⑤
Liu M2012[27]	53/41		6.8±1.4 (3-11)		A(63); B(25); Mixed(6)		Severity of icterus: 66(mild), 25(moderate), 3(severe)		40-60ml Compound glycyrrhizin injection dissolving in 250ml 5% glucose solution, ivgtt qd (+ Comparator)	Conventional western medicine (30ml PMA dissolving in 250ml 5% glucose solution, ivgtt qd; creatinine, vitC, energy mixture)	14	④⑤

A, Viral hepatitis type A; B, Viral hepatitis type B; C, Comparator group; ivgtt, intravenous drip; M, male; Mixed, mixed hepatitis; PMA, Potassium magnesium aspartate; qd, Once a day; T, Treatment (intervention) group.
Outcomes:
① ALT, Alanine aminotransferase
② AST, Aspartate aminotransferase
③ TBiL, Total bilirubin
④ Global improvement of symptoms
⑤ Duration of icterus.

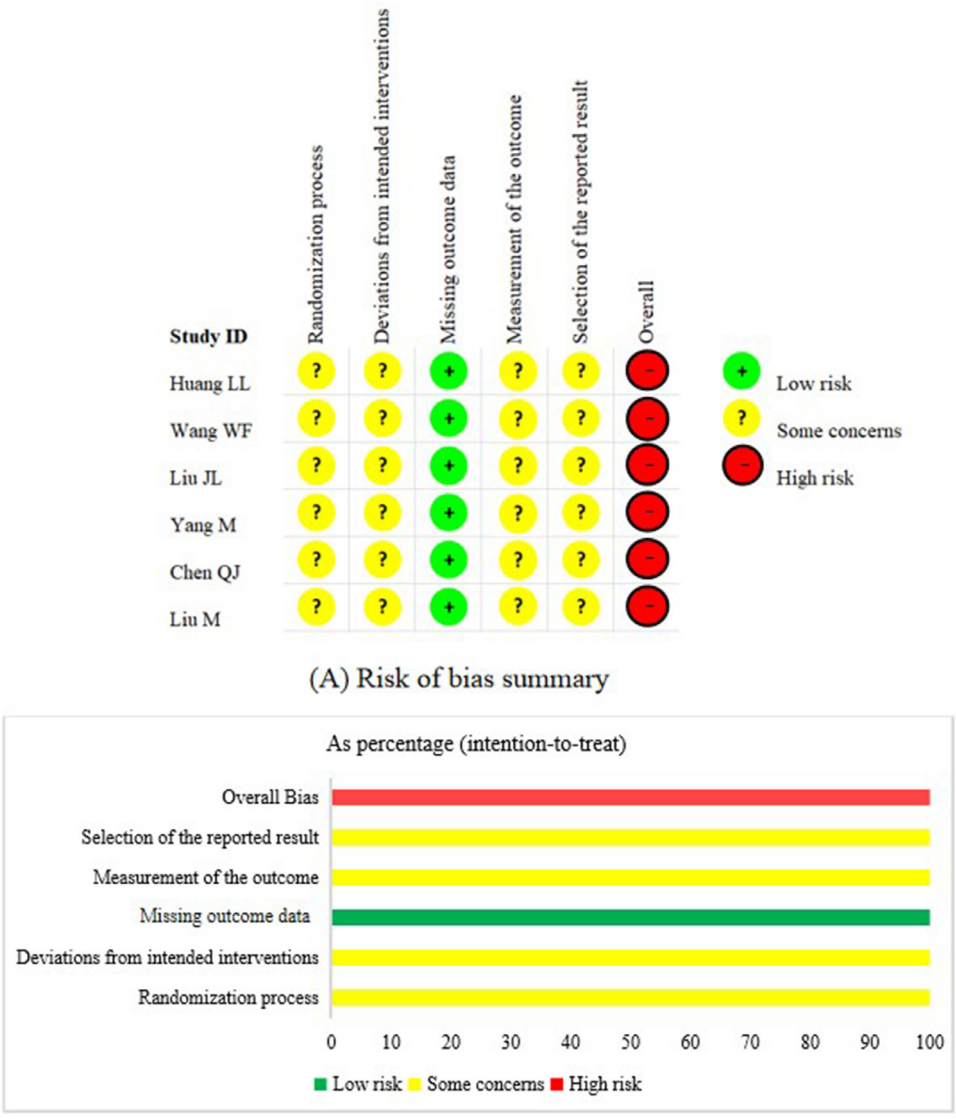

Fig. 2. Risk of bias for included trials.

information about deviations. Therefore, all trials[21–26] were judged as "some concerns" in this domain.

a) *Domain 3: Risk of bias due to missing outcome data*

All trials[21–26] were judged as "low risk of bias" in missing outcome data domain as the probably complete, or nearly complete outcome data available.

a) *Domain 4: Risk of bias in measurement of the outcome*

According to the interventions and comparators the included trials[21–26] reported, all trials[21–26] were impossible to blind the clinicians implementing treatments. What's more, all trials[21–26] did not report whether they blinded the outcome assessors, as well as they did not report the information of potential conflict of interest. Taking the above into consideration, all trials[21–26] were judged to be of "some concerns" in measurement of the outcome.

a) *Domain 5: Risk of bias in selection of the reported result*

No trial reported information on their trial protocol and registration. We could not judge whether these trials[21–26] have selectively reported outcomes. Therefore, all trials[21–26] were judged as "some concerns" in this domain.

According to the evaluation results of each domain, the overall bias was assessed as "high risk of bias" in all the included trials.

3.4. Outcomes

3.4.1. Primary outcomes (indexes related to liver function)

3.4.1.1. Total bilirubin (TBiL). A total of three trials[22–24] reported this outcome and reported the change in TBiL levels before and after treatment. A pooled result (Fig. 3-A) showed that there was a statistical difference between the intervention and the comparator groups (MD = -8.19 mmol/L, 95% CI -9.86 to -7.53, $P < 0.00001$), that is, CGI plus CWM was superior to CWM alone for AIHC in reducing the levels of TBiL.

3.4.1.2. Alanine aminotransferase (ALT). Four trials[21–24] reported the change of ALT levels. Meta-analysis (Fig. 3-B) showed that CGI plus CWM might be better than CWM alone in reducing the levels of ALT and there were statistical differences (MD = -24.09 U/L, 95% CI -30.83 to -17.34, $P < 0.00001$). Because of the large heterogeneity ($I^2 = 92\%$) between the four trials, we planned to explore the source of heterogeneity through subgroup analysis or sensitivity analysis. However, we failed to carry out relevant analyses owing

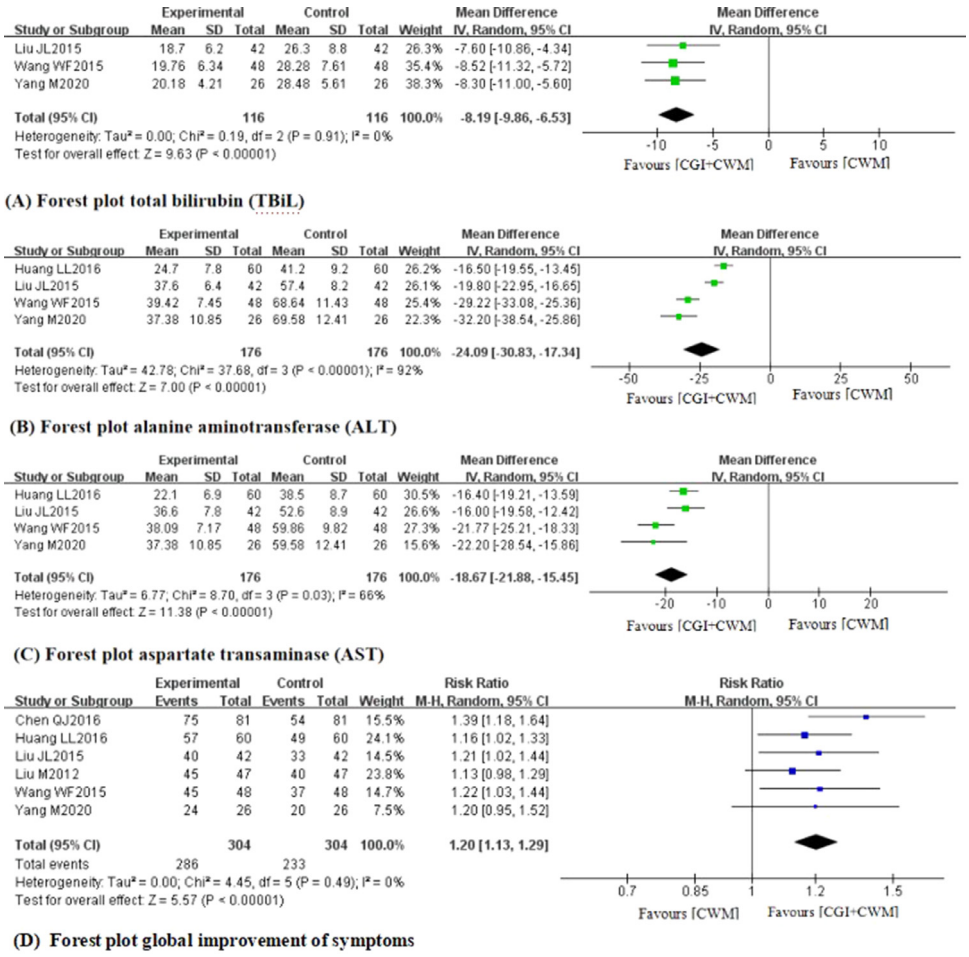

Fig. 3. Forest plots of outcomes.

to insufficient information provided by the included trials. Nevertheless, we considered that the large heterogeneity of statistics may be related to clinical heterogeneity (e.g., disease severity, different treatment courses, different drug doses, or some other clinical practice factors).

3.4.1.3. Aspartate transaminase (AST). Four trials[21–24] reported AST and all focused on the change in ALT levels before and after treatment. A result (Fig. 3-C) from the four trials showed that there was a statistical difference (MD = -18.67 U/L, 95% CI -21.88 to -15.45, $P < 0.00001$; large statistical heterogeneity, $I^2 = 66\%$) between intervention and comparator group, that is, CGI plus CWM may be better than CWM alone in reducing AST levels. An attempt to explore the source of large statistical heterogeneity subgroup analysis or sensitivity analysis was not possible due to the insufficient information being provided by the included trials.

3.4.2. Secondary outcomes

3.4.2.1. Global improvement of symptoms. All the included trials[21–26] reported this outcome. A pooled result (Fig. 3-D) showed that there was a statistical difference between the intervention and comparator groups in improving effective rate (RR = 1.20, 95% CI 1.13 to 1.29, $P < 0.00001$), that is, CGI plus CWM had better effects than CWM alone for AIHC on the global improvement of symptoms.

3.4.2.2. The disappearance rate or duration of icterus.

Disappearance rate of icterus

No trial reported on the outcome of icterus disappearance rate.

Duration of icterus

Two trials[25,26] reported the duration of icterus. Of these, one trial[25] showed that there was a statistical difference between intervention and comparator groups (MD -6.10 days, 95% CI -6.92 to -5.28, $P < 0.00001$), that is, CGI plus CWM was better than CWM alone in shortening the duration of icterus. The second trial[26] reported that "the duration of icterus in the intervention group was 6.5 ± 2.1days, which was significantly shorter than that in the comparator group".

3.4.2.3. Adverse events. None of the included trials reported this outcome.

3.5. Subgroup analysis

Due to the low number of publications and the lack of information reported in the publications, our review was unable to conduct subgroup analyses according to the preset conditions: the severity of AIHC, the different duration of treatment and the medication dosage of CGI.

3.6. Certainty of evidence (GRADE)

Using the GRADE system recommendation approach, the certainty of the evidence for outcomes were all evaluated as low or very low. The certainty of the evidence was downgraded mainly

Table 2
GRADE evaluation form of evidence certainty.

Patient or population: Acute Icteric Hepatitis in Children
Setting: Hospital
Intervention: Compound glycyrrhizin injection plus conventional western medicine
Comparator: Conventional western medicine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	The certainty of the evidence (GRADE)
	Risk with comparator	Risk with intervention			
TBiL		MD 8.19 lower (9.86 lower to 6.53 lower)	-	232 (3 RCTs) [22-24]	⊕⊕◯◯ LOW [a,b]
ALT		MD 24.09 lower (30.83 lower to 17.34 lower)	-	352 (4 RCTs) [21-24]	⊕◯◯◯ VERY LOW [a,b]
AST		MD 18.67 lower (21.88 lower to 15.45 lower)	-	352 (4 RCTs) [21-24]	⊕◯◯◯ VERY LOW [a,b]
global improvement of symptoms	766 per 1,000	920 per 1,000 (866 to 989)	RR 1.20 (1.13 to 1.29)	608 (6 RCTs) [21-26]	⊕⊕◯◯ LOW [a,b]
The duration of icterus		MD 6.1 lower (6.92 lower to 5.28 lower)	-	162 (1 RCT) [25]	⊕⊕◯◯ LOW [a,b]

* The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparator group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; RR: Risk ratio; Factors of downgrade:
[a] Risk of bias (high risk of detection bias and/or reporting bias)
[b] Inconsistency (significant statistical heterogeneity and/or small overlap of 95% CI of different trial results) GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

due to risk of bias (high risk of detection bias or reporting bias), inconsistency (significant statistical heterogeneity, or small overlap of 95% CI of different trial results). Table 2 provides a summary of the certainty of available evidence.

4. Discussion

4.1. Summary of the main findings

As mentioned earlier, one of the factors leading to AIHC is children's imperfect organ development and low immune system function. Moreover, AIHC can also lead to further impairment of liver function in children. The results of liver function examination for children with AIHC showed that the levels of children's total bilirubin (TBiL), alanine aminotransferase (ALT) and aspartate transaminase (AST) were significantly increased. Therefore, it is essential to improve the liver function of children with AIHC. In clinical practice, one of the important indexes for judging the improvement of liver function is whether the levels of TBiL, AST and TBIL decrease to a normal level. The results of our review demonstrated that CGI plus CWM was better than CWM alone in reducing the levels of TBiL, ALT and AST. That is, CGI may have adjuvant therapeutic effects on improving the liver function of children with AIHC.

In addition, the other treatment goals for children with AIHC are to eliminate the symptom of icterus and other symptoms (e.g., vomiting, fever, nausea). The results from one trial suggested that combining CGI with CWM was about six days shorter than for CWM alone for eliminating icterus. In terms of the global improvement of symptoms, CGI combined with CWM to treat AIHC is superior to that of CWM alone. A pooled result showed that the effective rate of global improvement of symptoms in the CGI group was 94.08% (286/304), which was approximately 17% higher than that of the control group (76.64%, 233/304), and was similar to the effective rate of all trials reporting this outcome (92.31% to 95.74%).

In conclusion, the use of CGI plus CWM in the treatment of AIHC may be an effective choice.

4.2. Implications for the clinical practice

All the interventions in the included trials compared CGI with CGI plus CWM. There were no trials included that examined the use of CGI alone to treat AIHC. The evidence in this review indicated that CGI may have adjuvant therapeutic effects on the treatment of children with AIHC. Therefore, we suggest that CGI, combined with CWM, could be useful in the treatment of AIHC. The CWM includes potassium magnesium aspartate, creatinine, vitamin C and/or energy mixtures, etc. However, whether CGI alone can be used to treat AIHC needs further study in the future.

The course of treatment for all the included studies was either 14 or 15 days duration. Therefore, we suggest that CGI could be used for at least 14 days in clinical practice. It is unclear whether a more prolonged the use of CGI will provide greater benefit to children. Safety of long term use also requires investigation. The dose of CGI ranged from 10 to 80 ml in light of the characteristics of the included trials. However, we failed to perform a subgroup analysis for different doses as planned, so the optimum number of doses to provide most benefit still needs clarification and is worthy of further exploration.

4.3. Strengths and limitations

This is the first systematic review, as far as we know, related to RCTs on the therapeutic effects and safety of CGI for AIHC. This review provides better evidence for clinical practice to further evaluate and verify the therapeutic effects of CGI for children with AIHC in improving their liver function. There are also limitations. No trial with low risk of bias was included and the sample sizes were small in the included trials and safety data was lacking.

4.4. Suggestions and implications for future research

According to the problems identified in the included RCTs, the following suggestions are proposed for future relevant RCTs,

(a) Use of an appropriate random allocation method (e.g., random number tables), with detailed reporting. In addition, the randomization should be properly concealed when participants are randomly assigned (e.g., numbered and light-tight sealed envelopes) to ensure the effective implementation of randomization.
(b) Ensure blinding of participants, physicians, outcome assessors and data analysts. The aims of blinding are to remove bias (per-

formance bias and detection bias).[27–29] For instance, participants and those evaluating the data from the trial do not have a preference for one treatment above another.[28]

(c) Use of the appropriate method to estimate the sample size of participants to ensure the reliability and validity of the study results.[30]

(d) Development of a detailed study protocol which is registered on the relevant website in advance. Related websites include clinicaltrials.gov (www.clinicaltrials.gov), Chinese ClinicalTrial Registry (ChiCTR, www.chictr.org/cn), and etc. The study protocol can be developed with reference to the SPIRIT 2013 Statement: Defining standard protocol items for clinical trials.[31,32] Meanwhile, it is suggested that a standardized report should be formulated with reference to the Consolidated Standards of Reporting Trials (CONSORT) statement.[33]

(e) The last and most important issue is about the safety of medication for children. As children are a special population, attention to the safety of children's medication is critical. However, according to the reports of outcomes in the included RCTs, the safety of CGI in the treatment of AIHC has not been given enough attention. Therefore, it is suggested that the safety of CGI used in AIHC should be evaluated and reported in the future.

4.5. Conclusion

Low or very low certainty evidence demonstrated that CGI has apparent adjuvant therapeutic effects on improving the liver function of children with AIHC. CGI plus CWM was better than CWM alone in reducing the levels of TBiL, ALT and AST, on the global improvement of symptoms and in shortening the duration of icterus. There was no evidence to determine the safety of CGI for AIHC.

As current evidence is weak, further well-designed RCTs are required for verification of the therapeutic effects of CGI.

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Author contributions

Conceptualization: JPL and SBL; Methodology: JPL, SBL and HJC; Software: SBL and WBH; Formal Analysis: SBL, WBH and HJC; Resources: SBL, WBH and CHL; Data Curation: SBL, WBH and HNW; Writing – Original Draft: SBL; Writing – Review & Editing: RXZ, LJY, HJC, MH, NR and JPL; Supervision: JPL; Project Administration: JPL and SBL; Funding Acquisition: JPL and NR. All authors have read and approved the manuscript, including the authorship list.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethical statement

This work did not require an ethical approval as it does not involve any human or animal experiment.

Data availability

The data used in this study are included in the article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100772.

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