The effect of Chinese herbal medicine on digestive system and liver functions should not be neglected in COVID-19: An updated systematic review and meta-analysis

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Abstract
Gastrointestinal symptoms and liver injury are common in patients with coronavirus disease 2019 (COVID-19). However, profiles of different pharmaceutical interventions used are relatively underexplored. Chinese herbal medicine (CHM) has been increasingly used for patients with COVID-19, but the efficacy of CHM used in COVID-19 on gastrointestinal symptoms and liver functions has not been well studied with definitive results based on the updated studies. The present study aimed at testing the efficacy of CHM on digestive symptoms and liver function (primary outcomes), the aggravation of COVID-19, and the time to viral assay conversion (secondary outcomes), among patients with COVID-19, compared with standard pharmacotherapy. The literature search was undertaken in 11 electronic databases from December 1, 2019 up to November 8, 2020. Appraisal of the evidence was conducted with Cochrane risk of bias tool or Newcastle Ottawa Scale. A random-effects model or subgroup analysis was conducted when significant heterogeneity was identified in the meta-analysis. The certainty of the evidence was assessed with the grading of recommendations assessment, development, and evaluation approach. Forty-eight included trials involving 4,704 participants were included. Meta-analyses favored CHM plus standard pharmacotherapy for COVID-19 on reducing the aggravation of COVID-19 and the time to viral assay conversion compared with standard pharmacotherapy. However, the present CHM as a complementary therapy for treating COVID-19 may not be beneficial for improving most gastrointestinal symptoms and liver function based on the current evidence. More well-conducted trials are warranted to confirm the potential efficacy of CHM furtherly.
1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world with substantial mortality since December 2019.\(^1\) To date, the potential treatment options to contain the disease include antiviral medications, steroids, antibacterial medications, human immunoglobulin, and so on. Chinese herbal medicine (CHM), as recommended in national treatment guidelines in China,\(^2\) has been increasingly used, and might pose a promising therapy for COVID-19.\(^3\)–\(^7\)

Some evidence of the efficacy of CHM for COVID-19 has emerged, suggesting that CHM may be used for COVID-19 in improving clinical symptoms, length of hospital stay, lung CT, and inflammatory biomarkers with fewer adverse events than conventional treatments.\(^8\),\(^9\) It was believed that CHM was an effective treatment for COVID-19 in Chinese health care system. However, the previous meta-analysis studying CHM for COVID-19 paid attention to respiratory tract manifestations and fever, without enough consideration on digestive symptoms and liver function. It was understandable that digestive symptoms and liver function were neglected in the previous COVID-19 studies since it was a race to find effective measures and it was of utmost necessity to control the most commonly depicted symptoms due to the sheer magnitude of the COVID-19 pandemic. However, the goal of evidence-based medicine is to provide comprehensive clinical practice suggestions, and the digestive symptoms and liver injury are not uncommon in patients with COVID-19.\(^10\) Emerging data have illustrated that the gastrointestinal tract and liver also represented target organs of SARS-CoV-2, according to the findings that angiotensin-converting enzyme 2, the major receptor of SARS-CoV-2, was also found in liver and gastrointestinal tract.\(^11\) Increased attention should be paid to digestive symptoms and liver function in COVID-19 patients.

CHM as an adjuvant for COVID-19 on gastrointestinal symptoms and liver functions has not been studied with definitive results based on the latest evidence assessment. Whether CHM may constitute a basis of drug treatment for COVID-19 patients with gastrointestinal symptoms and liver dysfunctions remains unclear. Although empirical use of CHM shows potential improvement, supporting evidence remains limited. We conducted a systematic review and meta-analysis of emerging studies reporting gastrointestinal symptoms and liver function in COVID-19 patients treated with CHM plus standard pharmacotherapy. As for the follow-up of adverse events that have been studied,\(^8\),\(^9\) we would not study it again.

2 | METHODS

This systematic review and meta-analysis, registered with the Open Science Framework (DOI: 10.17605/OSF.IO/8QCVP), was performed and reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Appendix S1).\(^12\)

2.1 | Literature search

A systematic literature search of the PubMed, ScienceDirect, Web of Science, Scopus, Google Scholar, WorldCat Dissertations database and Index to Theses, PsycINFO, ProQuest, the Chinese National Knowledge Infrastructure, the VIP Information Database, and the Wanfang Database was conducted on November 8, 2020 (updated February 9, 2021) for relevant articles including accepted pre-proof publications in the last 1 year, to identify the latest information on COVID-19. The following grouped terms were used as search strategy and modified to suit each database to screen publications that might be valuable for the present review: (“coronavirus disease 2019” OR “COVID-19” OR “severe acute respiratory syndrome coronavirus 2” OR “SARS-CoV-2” OR “coronavirus” OR “novel coronavirus” OR “nCoV” OR “2019-nCoV”) AND (“Medicine, Chinese Traditional” OR “Traditional Medicine, Chinese” OR “Chinese herbal medicine” OR “traditional Chinese medicine” OR “Chinese Traditional Medicine” OR “Chinese Medicine, Traditional” OR “Chinese medicine formulae” OR “Chinese medicine formulations” OR “Chinese herb” OR “Chinese herb therapy” OR “herbal medicine” OR “herb remedy” OR “herb therapy” OR “Zhong Yi Xue” OR “Chung I Hsueh” OR “Hsueh, Chung I”). Given the urgency of treating COVID-19, a gray literature search was also performed. Furthermore, COVID-19 articles in the WHO database and some key journals in this field including the New England Journal of Medicine, BMJ, the Lancet

KEYWORDS

coronavirus disease 2019, Chinese herbal medicine, gastrointestinal symptoms, liver function, meta-analysis
COVID-19 Resource Centre, and JAMA were searched manually for potentially relevant publications. Additional articles were retrieved by hand based on the reference lists of relevant papers. Search strategies were attached in the supplementary (Appendix S2).

2.2 | Eligibility criteria

2.2.1 | Types of studies

Application of CHM in COVID-19 patients was less evaluated through COVID-19 randomized controlled trials (RCTs), due to ethic, feasibility, and methodology issues. Observational studies were common sources of the literature evaluating the efficacy of CHM, considering the urgency of the topic. Accordingly, we included studies on humans, which were RCTs or observational studies with a control arm.

2.2.2 | Participants

Only patients with COVID-19 were considered in this study. To ensure that all relevant articles were included, we did not set any specifications for the ages, sexes, and ethnic origin of participants.

2.2.3 | Interventions

Participants in the treatment group should receive CHM as a co-intervention with standard pharmacotherapy. Participants in the control group should be treated by standard pharmacotherapy alone or standard pharmacotherapy plus placebo.

The definition of CHM was herbal agents and materials, that originated from botanical herbal products, mineral and animal sources, based on the Pharmacopoeia of the People’s Republic of China. Standard pharmacotherapy, namely the standard treatment, consisted of symptomatic control and supportive care for COVID-19, such as antiviral medications, antibacterial medications, steroids, and human immunoglobulin, mostly according to the evolving Chinese national COVID-19 treatment guidelines and hospital practice.

2.2.4 | Outcome measurement

The primary outcome measures were defined as gastrointestinal symptoms and liver functions. The main outcomes of gastrointestinal symptoms included the rate of nausea remission, remission of vomiting, rate of anorexia remission, and rate of diarrhea remission. The improvement rate of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as the main outcomes, represented liver function. The secondary outcome measures were defined as the aggravation of COVID-19, and the time to viral assay conversion.

2.3 | Exclusion criteria

The following studies were excluded: duplicate publications; review articles; editorials; case series without control group; viewpoints; commentaries; experimental in vitro studies; animal studies; expert opinions; studies pertaining to the suspected cases of COVID-19; and other complementary and alternative therapies beyond CHM, like massage, acupuncture, moxibustion, cupping, and music therapy, were contained in either CHM or control group; studies that did not report indicators to be discussed in this study.

2.4 | Study selection and data extraction

Two investigators (Shihua Shi and Jiang Li) independently searched the databases and screened the titles and abstracts. Disagreements about the eligibility and exclusion of a study were resolved via consensus or resolved by an arbitral reviewer (Zhenxing Wang). The following variables were independently extracted by two reviewers (Yulong Li and Xiaoping Wu) and cross-checked by another reviewer (Fei Wang): author; date; study design; patient demographics; severity of illness; interventions, and outcome parameters. We contacted the corresponding authors to resolve the incomplete data or data failed, attempting for more information, if possible.

2.5 | Risk of bias assessment

The Modification of Cochrane Tool to assess the risk of bias in randomized trials was used, in which the response options for each of the domains included “definitely or probably yes” (assigned a low risk of bias) and “definitely or probably no” (assigned a high risk of bias). The Newcastle Ottawa Scale (NOS) was used to assess the risk of bias of observational studies that met the inclusion criteria. The quality of enrolled studies was independently rated by two reviewers (Yongcan Wu and Xiaomin Wang). Any disagreements were resolved by discussion or resolved by a senior reviewer (Weihao Li).
2.6 | Data synthesis

The gastrointestinal symptoms including the remission rate of diarrhea, anorexia, nausea, and vomiting; liver function parameters including the improvement rate of ALT and AST; the rate of aggravation of COVID-19 and time to viral assay conversion were evaluated and merged. Meta-analysis of the outcomes above was conducted using the Cochrane Collaboration Review Manager software (RevMan, Version 5.3). The relative treatment effects of dichotomous data and continuous data were measured using risk ratio (RR) and mean difference (MD), respectively. The standard error was calculated from the 95% confidence interval (CI). Heterogeneity was explored using the Mantel–Haenszel $\chi^2$-test and $I^2$ statistic.18 The random-effects model was utilized to address the variation across the included studies, since the pooled studies may differ in study design, duration, disease type, severity, or others. Subject to the availability of a sufficient number of studies, subgroup analyses were performed according to the study design, specific prescriptions of interventions, disease type, severity, or duration to explain the heterogeneity issues identified before data analyses. We assessed publication bias using the funnel plot19 and the certainty of the evidence using the GRADEpro software.

3 | RESULTS

3.1 | Study selection process

Searches in the 11 databases yielded a total of 19,614 potential publications initially. 3,921 records remained after the removal of duplicates. The titles and abstracts of these papers were screened and 3,501 studies were dropped at this stage. The 420 studies, deemed to meet the criteria for full-text review, were retrieved for further eligibility assessment. Then, 375 of them failed to meet the inclusion criteria for various reasons (see Figure 1). Additional potentially relevant papers ($n = 3$) were identified through searches by hand in reference lists of reviews and included studies. Finally, 48 papers were appraised in the final stage (Table 1).

3.2 | Characteristics of studies included

In total, we analyzed 48 studies3–7,20–60 recruiting 4,704 patients with COVID-19. Of these, 2920,22–29,31,34–36,39,40,49–62 were observational studies with a control group, and 193–7,30,32,33,37,38,41–48,63 were RCTs included in the final analysis. Of these participants, 2,696 had been assigned to receive CHM as an adjuvant medicine, and 2,008 receive standard pharmacotherapy. CHM in most enrolled trials was orally administered. Other details were described in Table 1.

3.3 | Risk of bias in included studies

Table 2 summarized the risk of bias for the 19 RCTs.3–7,30,32,33,37,38,41–48,63 Sixteen studies described the method of randomization, employing computer software,4,6,7,30,33,37,38,41,42,44,46,48 or tossing a coin47 for randomization. Six RCTs3,4,30,47,48,63 were open-label studies because of the urgency of major public health events, subject to the risk of performance bias owing to the lack of placebo control. The other 13 studies2–7,32,33,37,38,41–46 did not mention the blinding of patients and personnel. Table 3 showed the NOS details for 29 observational studies.20,22–29,31,34–36,39,40,49–62 Eight observational studies20,22,24,26,34,49,50,57 were judged to be of moderate methodologic quality, subject to the unsatisfying risk of bias mostly owing to the lack of adequacy of follow up and completing accounting for observational studies.

3.4 | Outcome 1: Gastrointestinal symptoms

3.4.1 | Nausea remission

Of the 48 studies, six studies20,25,27–29,47 reported CHM on the rate of nausea remission in ordinary cases. No significant difference was found in the rate of nausea remission between the users and non-users of CHM (RR 1.04; 95% CI 0.83–1.30), and the heterogeneity was not significant ($I^2 = 0\%$, $p = 0.92$) (Figure 2a). We conducted subgroup analysis by study design, disease type, severity, or duration to explain the heterogeneity issues identified before data analyses. We assessed publication bias using the funnel plot19 and the certainty of the evidence using the GRADEpro software.

3.4.2 | Vomiting remission

Of the 48 studies, four studies28,29,34,47 reported CHM on the remission of vomiting. As shown in Figure 2b, there was no significant difference in the remission of vomiting between users and non-users of CHM (RR 1; 95% CI 0.77–1.29), and the heterogeneity was almost non-existent ($I^2 = 0\%$, $p = 1.00$). Similar result was observed in subgroup analysis conducted by study design, disease type, severity, or duration.
3.4.3 | Anorexia remission

Of the 48 studies, three controlled observational studies\(^{20,25,27}\) and three RCTs\(^{37,47,63}\) reported the rate of anorexia remission. Of the total 160 COVID-19 patients with anorexia, 75 received CHM along with standard pharmacotherapy and 85 received only standard pharmacotherapy. Three studies\(^{25,27,47}\) reported a reduction in the rate of anorexia and three\(^{20,37,63}\) did not report any benefit with the use of CHM compared with the controls. The heterogeneity was significant (\(I^2 = 87\%, \ p < 0.00001\)), which was likely due to variations across studies, and random-effects model was used to accommodate statistical heterogeneity.

As shown in Figure 2c, in the rate of anorexia remission, the combined treatment group outperformed standard pharmacotherapy alone (RR 2.09; 95% CI 1.04–4.19), with an improved disappearance rate of anorexia. We conducted subgroup analysis when ≥2 studies could be pooled, and a similar result was observed in the subgroup of observational studies.

3.4.4 | Diarrhea remission

Twelve studies explored the rate of diarrhea remission after the use of CHM for COVID-19. Six of them\(^{6,7,32,37,47,63}\) were
| References                | Age (mean ± SD or age range (years)) | Male/female | Severity of illness | Patients (n) | Loss to follow-up | Outcome |
|---------------------------|-------------------------------------|-------------|---------------------|--------------|-------------------|---------|
| Ai et al., 2020a          | 18–75                               | 40/27       | Ordinary cases      | 33/34        | 0                 | ③      |
| Chen, Li et al., 2021a    | T: 50.16 ± 5.11 C: 49.52 ± 5.06     | 35/25       | Ordinary cases      | 30/30        | 2/1               | ③      |
| Ding et al., 2020a        | Age ≥ 18                            | 78/22       | All stages of COVID | 51/49        | 0                 | ③      |
| Duan et al., 2020a        | T: 51.99 ± 13.88 C: 50.29 ± 13.17   | 62/61       | Mild COVID-19       | 96/48        | 14/7              | ③      |
| Fu et al., 2020a          | T: 43.26 ± 7.15 C: 43.68 ± 6.45     | 36/29       | Ordinary cases      | 32/33        | 0                 | ③      |
| Hu F. et al., 2020a       | 18–75                               | 104/96      | Ordinary cases      | 100/100      | 43/29             | ③      |
| Hu K. et al., 2020a       | T: 50.4 ± 15.2                      | 150/134     | All stages of COVID | 142/142      | 3/3               | ③      |
|                          | C: 51.8 ± 14.8                      |             |                     |             |                   |         |
| Lan et al., 2020a         | T: 43.05 ± 13.26 C: 42.40 ± 13.47   | 64/21       | Ordinary cases      | 43/42        | 0                 | ③      |
| Liao, 2020a               | T: 65.25 ± 7.42 C: 67.16 ± 8.64     | 38/32       | All stages of COVID | 35/35        | 0                 | ③      |
| Lin F. et al., 2020a      | T: 46.02 ± 12.09 C: 43.80 ± 12.34   | 38/44       | Ordinary cases      | 41/41        | 0                 | ③      |
| Ping et al., 2021a        | T: 23–58                           | 26/28       | Ordinary cases      | 30/30        | 0/6               | ③      |
|                          | C: 25–64                           |             | Mild COVID-19       |             |                   |         |
| Qiu et al., 2020a         | T: 53.35 ± 18.35 C: 51.32 ± 14.62   | 27/23       | Ordinary cases      | 25/25        | 0                 | ③      |
| Sun et al., 2020a         | T: 45.4 ± 14.10 C: 42.0 ± 11.70     | 28/29       | Ordinary cases      | 32/25        | 0                 | ③      |
| Wang L. et al., 2020a     | T: 41.1 ± 14.5 C: 40.8 ± 13.7        | 51/29       | Ordinary cases      | 40/40        | 0                 | ③      |
| Wang YL. et al., 2020a    | 4–70                                | 11/11       | Asymptomatic SARS- CoV-2 Infection | 11/11 | 0 | ③ |
| Xiao et al., 2020a        | T: 54.58 ± 13.76 C: 54.06 ± 13.90   | 70/51       | All stages of COVID-19 | 58/63 | 0 | ③ |
|                          |                                     |             |                     |             |                   |         |
| Xiong et al., 2020a       | T: 57.10 ± 14.00 C: 62.40 ± 12.3    | -           | Mild to severe stages of COVID-19 | 22/20 | 0 | ③ |
| Ye et al., 2020a          | T: 65 (53.5–69) C: 59 (47–67)       | 6/35        | All stages of COVID-19 | 28/14 | 0 | ③ |
| References          | Age (mean ± SD) or age range (years) | Male/ female | Severity of illness | Patients (n) | Loss to follow-up | Outcome |
|---------------------|-------------------------------------|--------------|---------------------|--------------|-------------------|---------|
|                     |                                     |              |                     | CHM group    | Control group     | T/C     |
| Yu P. et al., 2020  | T: 48.27 ± 9.56 C: 47.25 ± 8.67    | 171/124      | Mild COVID-19       | 147          | 148               | 0       |
| Chen, Chen et al., 2020 | 23–95                          | 102/128      | Ordinary cases      | 115          | 115               | 0       |
| Chen, Liu et al., 2020 | Age ≥18                        | 29/39        | Ordinary cases      | 34           | 34                | 0       |
| Cheng D. et al., 2020 | 18–70                         | 53/49        | Ordinary cases      | 51           | 51                | 0       |
| Cheng L. et al., 2020 | 20–91                         | 300/316      | Severe COVID-19 Pneumonia | 499         | 117               | 0       |
| Guo et al., 2020  | T: 52 (46–57) C: 54 (44–59)      | 20/12        | Mild to severe stages of COVID-19 | 16          | 16                | 0       |
| Hu Y. et al., 2020  | T: 48.30 ± 16.56 C: 49.75 ± 17.15 | 34/18       | All stages of COVID-19 | 31          | 21                | 0       |
| Huang et al., 2020  | T: 58.4 ± 15.5 C: 66.3 ± 14.1    | 22/23        | All stages of COVID-19 | 30          | 15                | 0       |
| Ji et al., 2020    | 18–70                              | 28/22        | Ordinary cases      | 28           | 22                | 0       |
| Ke et al., 2020    | T: 56.17 ± 13.35 C: 52.43 ± 10.12 | 59/44        | Ordinary cases      | 81           | 22                | 0       |
| Li et al., 2020    | T: 53.60 ± 0.26 C: 50.43 ± 0.34   | 28/32        | All stages of COVID | 30           | 30                | 0       |
| Lian et al., 2020  | T: 61.3 ± 14.11 C: 58.07 ± 11.98 | 25/39        | All stages of COVID | 38           | 26                | 0       |
| Lin Y. et al., 2020 | T: 51.67 ± 17.69 C: 43.36 ± 13.11 | 22/21        | All stages of COVID | 18           | 25                | 0       |
| Lin Z. et al., 2020 | 45.46 ± 14.87                    | 28/40        | Ordinary cases      | 51           | 17                | 0       |
| Liu et al., 2020   | T: 44.06 ± 14.23 C: 49.85 ± 17.10 | 17/15        | Ordinary cases      | 18           | 14                | 0       |
| Pan et al., 2020   | 60.01 ± 13.00                     |              | Severe and critical COVID-19 Pneumonia | 26          | 14                | 0       |

(Continues)
RCTs, and six of them were controlled observational studies. Of the total 187 COVID-19 patients with diarrhea, 96 received CHM along with standard pharmacotherapy and 91 received only standard pharmacotherapy. The pooled analysis did not show any significant difference in the rate of diarrhea remission between

| References                  | Age (mean ± SD) or age range (years) | Male/female | Severity of illness                     | Patients (n) | Loss to follow-up | Outcome |
|-----------------------------|--------------------------------------|-------------|-----------------------------------------|--------------|------------------|---------|
| Qin et al., 2020b           | T: 58.0 ± 2.9                        | 25/22       | Severe COVID-19 Pneumonia              | 21           | 26               | 0       |
|                             | C: 58.3 ± 2.9                        |             |                                         |              |                  |         |
| Qu et al., 2020b            | T: 40.65 ± 8.23                      | 41/29       | COVID-19                                | 40           | 30               | 0       |
|                             | C: 39.82 ± 6.40                      |             |                                         |              |                  |         |
| Shi et al., 2020b           | 47.61 ± 15.18                        | 36/31       | All stages of COVID-19                 | 49           | 18               | 0       |
| Song et al., 2020b          | T: 18–80                             | 31/29       | Ordinary cases                          | 30           | 30               | 0       |
|                             | C: 21–80                             |             | Mild COVID-19                           |              |                  |         |
| Su et al., 2020b            | 17–86                                | 82/68       | Ordinary cases                          | 75           | 75               | 0       |
|                             |                                     |             | Mild COVID-19                           |              |                  |         |
| Wang L. et al., 2020b       | T: 44.68 ± 11.42                     | 38/49       | All stages of COVID                    | 47           | 40               | 0       |
|                             | C: 49.70 ± 13.13                     |             |                                         |              |                  |         |
| Wang YY. et al., 2020b      | T: 65 (61–68)                        | 39/47       | Severe COVID-19                         | 43           | 43               | 0       |
|                             | C: 66 (56–71)                        |             |                                         |              |                  |         |
| Xia et al., 2020b           | 23–83                                | 23/29       | All stages of COVID                    | 34           | 18               | 0       |
|                             |                                     |             |                                         |              |                  |         |
| Xu et al., 2020b            | T: 52.42 ± 15.7                      | 23/29       | Ordinary cases                          | 26           | 26               | 0       |
|                             | C: 52.04 ± 13.41                     |             |                                         |              |                  |         |
| Yao et al., 2020b           | Age ≥18                              | 28/14       | Ordinary cases                          | 21           | 21               | 0       |
|                             |                                     |             |                                         |              |                  |         |
| Yu X. et al., 2020c         | T: 60.50 ± 2.08                      | 39/50       | All stages of COVID                    | 43           | 46               | 0       |
|                             | C: 64.23 ± 2.51                      |             |                                         |              |                  |         |
| Zeng et al., 2020b          | T: 46.65 ± 6.21                      | 124/105     | COVID-19 pneumonia with Phlegm-heat obstructing lung | 104          | 125              | 0       |
|                             | C: 46.21 ± 5.62                      |             |                                         |              |                  |         |
| Zhang H. et al., 2020c      | T: 43.4 ± 15.9                       | 8/14        | COVID-19                                | 11           | 11               | 0       |
|                             | C: 40.7 ± 13.3                       |             |                                         |              |                  |         |
| Zhang N. et al., 2020b      | T: 51.7 ± 12.5                       | 62/58       | Ordinary cases                          | 90           | 30               | 0       |
|                             | C: 49.2 ± 13.6                       |             |                                         |              |                  |         |

Note: ①, Disappearance rate of nausea; ②, Disappearance rate of vomiting; ③, Disappearance rate of anorexia; ④, Disappearance rate of diarrhea; ⑤, Alanine aminotransferase; ⑥, Aspartate aminotransferase; ⑦, Aggravation of COVID-19; ⑧, Time of nucleic acid conversion to negative.
Abbreviations: C, control group; CHM, Chinese herbal medicine; SD, standard deviation; T, treatment group.

Randomized controlled trial.
Cohort study.
Case-Control Study.
the CHM and standard pharmacotherapy (RR 1.04; 95% CI 0.92–1.16; I² = 0%) (Figure 2d). Similar results were observed in the subgroup analysis by study design, prescriptions of interventions, disease type, severity, or duration when ≥2 studies could be pooled in the subgroup.

### Table 2 Risk of bias assessment of RCTs

| References      | Adequate randomization sequence generation | Adequate allocation concealment | Blinding of patients | Blinding of health care providers | Blinding of data collectors | Blinding of outcome assessors | Blinding of data analyst | Loss to follow-up (%) |
|-----------------|-------------------------------------------|--------------------------------|----------------------|----------------------------------|-----------------------------|-----------------------------|------------------------|------------------------|
| Ai et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Chen, Li et al., 2021 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Ding et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Duan et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 14.6                   |
| Fu et al., 2020  | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Hu F. et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 36.0                   |
| Hu K. et al., 2020 | Yes                                       | Probably yes                   | No                   | No                               | Probably no                 | Probably no                 | Probable yes           | 2.1                    |
| Lan et al., 2020 | Probably no                                | Probably no                    | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Liao, 2020      | Probably yes                               | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Lin F. et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Ping et al., 2021 | Probably no                                | Probably no                    | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Qiu et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Sun et al., 2020 | Yes                                       | Probably yes                   | No                   | No                               | Probably no                 | Probably no                 | Probably yes           | 0                      |
| Wang L. et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Wang YL. et al., 2020 | Yes                                       | Probably yes                   | No                   | No                               | Probably no                 | Probably yes                | Probably yes           | 0                      |
| Xiao et al., 2020 | Yes                                       | Probably yes                   | No                   | No                               | Probably no                 | Probably yes                | Probably yes           | 0                      |
| Xiong et al., 2020 | Probably no                                | Probably yes                   | No                   | No                               | Probably no                 | Probably yes                | Probably yes           | 0                      |
| Ye et al., 2020  | Yes                                       | Yes                            | No                   | No                               | Yes                         | Yes                         | Yes                    | 0                      |
| Yu P. et al., 2020 | Yes                                       | Probably yes                   | Probably no          | Probably yes                     | Probably yes                | Probably yes                | Probably yes           | 0                      |
| Study ID          | Selection Representativeness of exposed cohort | Selection Representativeness of the non-exposed cohort | Ascertainment of exposure | Outcome Demonstration that outcome of interest was not present at the start of study | Comparability A | B | Assessment of outcome | Follow-up | Complete accounting for cohorts | Total | Quality |
|------------------|-----------------------------------------------|-------------------------------------------------------|---------------------------|---------------------------------------------------------------------------------|-----------------|---|-----------------------|------------|---------------------------------|-------|----------|
| Chen, Chen et al., 2020 | 1                                              | 1                                                      | 1                         | 0                                                                                | 1       | 1 | 1                    | 1          | 0                              | 7     | High     |
| Chen, Liu et al., 2020 | 1                                              | 1                                                      | 1                         | 0                                                                                | 1       | 1 | 1                    | 1          | 0                              | 7     | High     |
| Cheng D. et al., 2020 | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 0 | 1                    | 1          | 0                              | 7     | High     |
| Cheng L. et al., 2020 | 1                                              | 1                                                      | 1                         | 1                                                                                | 0       | 1 | 1                    | 1          | 0                              | 7     | High     |
| Guo et al., 2020   | 1                                              | 1                                                      | 1                         | 0                                                                                | 0       | 0 | 1                    | 1          | 0                              | 5     | Moderate |
| Hu Y. et al., 2020  | 1                                              | 1                                                      | 1                         | 1                                                                                | 0       | 1 | 1                    | 0          | 0                              | 6     | Moderate |
| Huang et al., 2020  | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 1          | 0                              | 8     | High     |
| Ji et al., 2020    | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 0 | 1                    | 1          | 0                              | 7     | High     |
| Ke et al., 2020    | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 0 | 1                    | 0          | 0                              | 6     | Moderate |
| Li et al., 2020    | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 0          | 0                              | 7     | High     |
| Lian et al., 2020  | 1                                              | 1                                                      | 1                         | 0                                                                                | 1       | 1 | 1                    | 1          | 0                              | 7     | High     |
| Lin Y. et al., 2020 | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 1          | 0                              | 8     | High     |
| Lin Z. et al., 2020 | 1                                              | 1                                                      | 1                         | 0                                                                                | 1       | 1 | 1                    | 1          | 0                              | 6     | Moderate |
| Liu et al., 2020   | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 1          | 0                              | 8     | High     |
| Pan et al., 2020   | 0                                              | 1                                                      | 1                         | 0                                                                                | 1       | 1 | 1                    | 0          | 0                              | 5     | Moderate |
| Qin et al., 2020   | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 1          | 0                              | 8     | High     |
| Qu et al., 2020    | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 1          | 0                              | 8     | High     |
| Shi et al., 2020   | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 1          | 0                              | 8     | High     |
| Song et al., 2020  | 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 0          | 0                              | 7     | High     |
| Su et al., 2020    | 1                                              | 1                                                      | 1                         | 1                                                                                | 0       | 1 | 1                    | 1          | 0                              | 7     | High     |
| Wang L. et al., 2020| 1                                              | 1                                                      | 1                         | 1                                                                                | 1       | 1 | 1                    | 0          | 0                              | 7     | High     |
### 3.5 | Outcome 2: The recovery of liver function

#### 3.5.1 | Alanine aminotransferase

The effective rate of ALT returning to normal was examined by three controlled observational studies, and one RCT. As shown in Figure 3a, there was no significant difference in the effective rate of ALT returning to normal between the users and non-users of CHM (RR 1.23; 95% CI 0.91–1.65; $\chi^2 = 54\%$). Subgroup analysis could not be conducted since the number of studies was limited.

#### 3.5.2 | Aspartate aminotransferase

The effective rate of AST returning to normal was examined by three controlled observational studies, and one RCT. As shown in Figure 3b, there was no significant difference in AST between the users and non-users of CHM (RR 1.22; 95% CI 0.92–1.61; $\chi^2 = 68\%$). We could not perform further subgroup analysis because of the limited number of studies.

### 3.6 | Outcome 3: Efficacy on COVID-19

#### 3.6.1 | Aggravation of COVID-19

The aggravation of COVID-19 among users and non-users of CHM for COVID-19 was assessed by 28 studies including 12 RCTs and 16 controlled observational studies. Of the total 3,415 COVID-19 patients included, 2,011 received CHM along with standard pharmacotherapy and 1,404 received only standard pharmacotherapy. The meta-analysis showed significant difference between the two groups (RR 0.43; 95% CI 0.34–0.55), with almost non-existent heterogeneity ($\chi^2 = 0\%$; $p = 0.80$) (Figure 4a). These results were consistent with those in the subgroups conducted by study design, disease type, severity, prescriptions of interventions, and duration.

#### 3.6.2 | Time to viral assay conversion

Time to viral assay conversion was reported by 19 studies including 13 controlled observational studies.
and six RCTs. Of the total 1,349 COVID-19 patients included, 712 received CHM along with standard pharmacotherapy and 637 received only standard pharmacotherapy. It was found that CHM plus standard pharmacotherapy had a shorter time to viral assay conversion than the comparators (MD $-3.48; 95\% \text{ CI } -4.33$ to $-2.64$) with significant heterogeneity ($I^2=84\%; p<0.00001$), and random-effects model was used to accommodate statistical heterogeneity (Figure 4b). These results were consistent with those in the subgroups conducted by study design, duration, disease type, and severity.

3.7 | Publication bias

Potential publication bias was found by the visual inspection of the funnel plot in the meta-analysis of CHM’s effects on the aggravation of COVID-19. The funnel plot was asymmetric, suggesting a mild publication bias of this meta-analysis (Figure 5).

3.8 | Certainty of the evidence

The certainty of evidence relevant to the aggravation of COVID-19 in RCTs had high quality. Diarrhea remission in RCTs, anorexia remission in observational trials, and the aggravation of COVID-19 in observational trials had a moderate quality of evidence. The certainty of evidence relevant to the following outcomes was low: the rate of nausea remission, anorexia remission, and vomiting remission in RCTs; the effective rate of ALT and AST returning to normal in RCT; the rate of nausea remission, and diarrhea remission in observational trials. Additionally, the quality of findings relevant to the time to viral assay conversion, the remission of vomiting in observational trials, and the effective rate of ALT and AST returning to normal in observational trials, was very low, suggesting that those outcomes should be interpreted carefully and may be changed after future researches (Table 4).

4 | DISCUSSION

According to the data released by WHO, as of 11:21 pm on 29 November 2020, there were 61,869,330 confirmed COVID-19 cases and 1,448,896 confirmed deaths in 220 countries, areas, or territories. A vast number of clinical studies have reported about COVID-19 treatment. Several initial observational studies were reported in rapid succession with poor methodologic quality, and most did not report outcomes of gastrointestinal symptoms and liver function. Nevertheless, COVID-19 patients experienced gastrointestinal symptoms, such as anorexia, nausea, vomiting, and diarrhea; they may also present with abnormal liver functions, which manifested as an increase in ALT and AST; digestive symptoms and liver
injury became more pronounced as the severity of the disease increased.\textsuperscript{65} Hence, identifying the efficacy of potential therapeutics not only on COVID-19 but also on gastrointestinal symptoms and liver function, needed to be considered.

Among the various medications tried, CHM has received noticeable attention. Traditional Chinese medicine believed patients can be diagnosed and generalized into certain patterns according to clinical manifestations, and treated with herbal medicine. With the increasing relevant evidence including RCTs, we investigated the pooled efficacy of CHM on gastrointestinal symptoms and liver function in patients with COVID-19, and found that CHM plus standard pharmacotherapy may reduce the rate of COVID-19 aggravation and the nucleic acid-negative conversion time, but did not improve liver functions, compared with standard pharmacotherapy. In addition, the present CHM aimed at COVID-19 had no advantages on most gastrointestinal symptoms compared with standard pharmacotherapy, which may be caused by the large number of applications of cold-natured herbs with the function of clearing away heat and removing toxins to treat the emergency symptoms of COVID-19.

\textbf{FIGURE 3} Forest plot of the comparison of CHM versus standard pharmacotherapy for the outcome of liver function

(a) The effective rate that ALT level returned to normal

| Study or Subgroup | Experimental Events Total | Control Events Total | Weight | Risk Ratio M-H. Random 95% CI | Risk Ratio M-H. Random 95% CI |
|-------------------|--------------------------|---------------------|--------|-------------------------------|-------------------------------|
| Observational trials | 5 \hspace{1cm} 10 | 7 \hspace{1cm} 8 | 13.6% | 0.57 [0.20, 1.12] | |
| Pan GT et al. 2020 | 22 \hspace{1cm} 26 | 8 \hspace{1cm} 14 | 21.2% | 1.48 [0.91, 2.40] | |
| Xia WG et al. 2020 | 31 \hspace{1cm} 34 | 11 \hspace{1cm} 18 | 26.8% | 1.49 [1.02, 2.19] | |
| Subtotal (95% CI) | 70 \hspace{1cm} 40 | 61.8% | 1.15 [0.68, 1.93] | |
| Total events | 58 \hspace{1cm} 26 | | | |
| Heterogeneity: Tau² = 0.14; Chi² = 6.48, df = 2 (P = 0.04); I² = 69% | |
| Test for overall effect: Z = 0.52 (P = 0.60) | |

(b) The effective rate that AST level returned to normal

| Study or Subgroup | Experimental Events Total | Control Events Total | Weight | Risk Ratio M-H. Random 95% CI | Risk Ratio M-H. Random 95% CI |
|-------------------|--------------------------|---------------------|--------|-------------------------------|-------------------------------|
| Observational trials | 10 \hspace{1cm} 12 | 10 \hspace{1cm} 10 | 27.0% | 0.85 [0.83, 1.14] | |
| Pan GT et al. 2020 | 24 \hspace{1cm} 26 | 8 \hspace{1cm} 14 | 18.6% | 1.62 [1.01, 2.58] | |
| Xia WG et al. 2020 | 29 \hspace{1cm} 34 | 10 \hspace{1cm} 18 | 19.6% | 1.54 [0.99, 2.37] | |
| Subtotal (95% CI) | 72 \hspace{1cm} 42 | 65.5% | 1.25 [0.75, 2.10] | |
| Total events | 63 \hspace{1cm} 28 | | | |
| Heterogeneity: Tau² = 0.17; Chi² = 10.20, df = 2 (P = 0.006); I² = 80% | |
| Test for overall effect: Z = 0.88 (P = 0.39) | |

| Study or Subgroup | Experimental Events Total | Control Events Total | Weight | Risk Ratio M-H. Random 95% CI | Risk Ratio M-H. Random 95% CI |
|-------------------|--------------------------|---------------------|--------|-------------------------------|-------------------------------|
| RCT | 40 \hspace{1cm} 41 | 33 \hspace{1cm} 41 | 34.5% | 1.21 [1.03, 1.42] | |
| Subtotal (95% CI) | 40 \hspace{1cm} 33 | 34.5% | 1.21 [1.03, 1.42] | |
| Total events | 113 \hspace{1cm} 83 | 100.0% | 1.22 [0.92, 1.61] | |
| Heterogeneity: Tau² = 0.05; Chi² = 0.50, df = 3 (P = 0.02); I² = 68% | |
| Test for overall effect: Z = 1.37 (P = 0.17) | |
| Test for subgroups differences: Chi² = 0.01, df = 1 (P = 0.90), I² = 0% | |
This study has several strengths. Firstly, this meta-analysis systematically assessed the efficacy of CHM on gastrointestinal symptoms and liver functions among COVID-19 patients through analysis of both RCTs and observational studies based on the latest studies, providing a comprehensive synthesis of up-to-date evidence. Our findings underlined the need of paying attention to COVID-19 patients who were suffering gastrointestinal

(a) Aggravation of COVID-19

(b) Nucleic acid-negative conversion time
symptoms and liver injury, which may inspire future COVID-19 studies. Besides, we conducted subgroup analysis according to study design, duration, prescriptions of interventions, disease type, and severity to rule out the influence of variations and eliminate heterogeneity. In addition, we evaluated the current results based on the grading of recommendations assessment, development, and evaluation (GRADE) assessment, which may be beneficial to the revision and promotion of the new diagnosis and treatment guidelines in the later stage.

Nevertheless, some limitations should be noted in our meta-analysis. First, most of our included studies were conducted in China. Limited information on other ethnic groups may have admission bias and selection bias. Second, as for the controlled observational studies included, some confounding factors may influence the certainty of the evidence. The sample size of some studies was small, so the test efficiency of some outcomes may be insufficient. Third, clinical studies evaluating the efficacy of CHM on COVID-19 usually had several limitations such as no placebo and poor methodologic quality.

In view of the public anxiety on COVID-19 worldwide, this systematic review and meta-analysis, critically appraising CHM and presenting evidence, may provide some evidence on this important issue. CHM achieved synergistic efficacy in reducing the rate of COVID-19 aggravation and the time to viral assay conversion when combined with standard pharmacotherapy when compared with standard pharmacotherapy, which may give meaningful hints to the clinical practice, and inspiration for the development of new drugs. Our results may allow clinicians and COVID-19 patients to comprehensively understand the efficacy of CHM on the digestive system and liver functions and make informed decisions. Certainly, the CHM that aimed at COVID-19 with a protective effect on the liver and digestive system needs to be investigated furtherly. Due to the limited understanding of the mechanism and precise therapeutic components of CHM, the standardization or evidence-based rationale for CHM used in COVID-19 still needs further studies. Additionally, the relevant placebo-controlled trials with double-blind are warranted in future COVID-19 researches.

5 CONCLUSION

This meta-analysis of CHM on gastrointestinal symptoms and liver function for COVID-19 patients seemingly indicated that although CHM had some benefits in reducing the rate of COVID-19 aggravation and nucleic acid-negative conversion time, the present CHM against COVID-19 showed limited advantages in improving gastrointestinal symptoms and liver function in conjunction with conventional medical care for COVID-19 patients, based on the latest evidence. Further exploration of current findings and well-conducted trials are warranted.

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CONFLICT OF INTEREST

The authors have declared that no competing interest exists.

AUTHOR CONTRIBUTIONS

Shihua Shi and Zhenxing Wang conceived the study. Zhenxing Wang and Fei Wang supervised the overall study. Shihua Shi, Jiang Li, and Yulong Li drafted the manuscript and produced the tables and pictures. Shihua Shi and Jiang Li separately performed the literature searches. Yulong Li and Xiaoping Wu separately conducted the data extraction of each of the included studies. Yongcan Wu, Caixia Pei, Demei Huang, and Xiaomin Wang conducted methodological quality evaluation of the eligible studies. Jiang Li and Heng Qiu conducted statistical analysis. Peili Wang, Weihao Li, Shuo Kou, and Zhenxing Wang critically revised the manuscript for important intellectual content. All the authors participated in making the decision to submit the manuscript for publication.

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## TABLE 4  Certainty of evidence

| No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of patients | Effect | Relative (95% CI) | Absolute | Quality | Importance |
|----------------|--------|--------------|---------------|--------------|-------------|---------------------|-----------------|--------|-----------------|-----------|---------|------------|
| **Disappearance rate of nausea—Observational trials** | | | | | | | 5  | | | | | |
| 5  | Observational studies | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | None | 18/24  (75%) | 16/22  (72.7%) | RR 1.04  (0.82 to 1.31) | 29 more per 1000 (from 131 fewer to 225 more) | LOW  | CRITICAL |
| | | | | | | | 66.7% | | | | | |
| **Disappearance rate of nausea—RCT** | | | | | | | 1  | | | | | |
| 1  | Randomised trials | Serious  | No serious inconsistency | No serious indirectness | Serious  | None | 4/6  (66.7%) | 3/5  (60%) | RR 1.11  (0.45 to 2.77) | 66 more per 1000 (from 330 fewer to 1000 more) | LOW  | CRITICAL |
| | | | | | | | 66% | | | | | |
| **Disappearance rate of vomiting—Observational trials** | | | | | | | 3  | | | | | |
| 3  | Observational studies | No serious risk of bias | No serious inconsistency | No serious indirectness | Serious  | None | 10/10  (100%) | 9/9  (100%) | RR 1  (0.77 to 1.3) | 0 fewer per 1000 (from 230 fewer to 300 more) | VERY LOW  | CRITICAL |
| | | | | | | | 100% | | | | | |
| **Disappearance rate of vomiting—RCT** | | | | | | | 1  | | | | | |
| 1  | Randomised trials | Serious  | No serious inconsistency | No serious indirectness | Serious  | None | 2/3  (66.7%) | 2/3  (66.7%) | RR 1  (0.32 to 3.1) | 0 fewer per 1000 (from 453 fewer to 1000 more) | LOW  | CRITICAL |
| Quality assessment                          | No. of patients | Effect                                      |
|--------------------------------------------|-----------------|---------------------------------------------|
| Disappearance rate of anorexia—Observational trials |                 |                                             |
| 5 Observational studies                     | 66.7%           | 0 fewer per 1000 (from 454 fewer to 1000 more) |
| No serious risk of bias                     | 16.7%           | 387 more per 1000 (from 17 more to 1000 more) |
| No serious indirectness                    |                 |                                             |
| No serious imprecision                      |                 |                                             |
| Strong association\(^d\)                    |                 |                                             |
| Plus vs. CPT                                | Control         | Relative (95% CI) Absolute Quality Importance |
| 28/37 (75.7%)                               | 11/53 (20.8%)   | RR 3.32 (1.1 to 9.98) | LOW CRITICAL |
| 482 more per 1000                          | 192 more per 1000 | (from 21 more to 1000 more) \(\uparrow\) |
| Disappearance rate of anorexia—RCTs         |                 |                                             |
| 3 Randomised trials                         | 83.3%           | 233 more per 1000 (from 192 fewer to 93.3 more) |
| No serious risk of bias                     |                 |                                             |
| No serious indirectness                    |                 |                                             |
| No serious imprecision                      |                 |                                             |
| Strong association\(^d\)                    |                 |                                             |
| Plus vs. CPT                                | Control         | Relative (95% CI) Absolute Quality Importance |
| 34/38 (89.5%)                               | 22/32 (68.8%)   | RR 1.28 (0.77 to 2.12) | MODERATE CRITICAL |
| 192 more per 1000                          | 233 more per 1000 | (from 158 fewer to 770 more) \(\uparrow\) |
| Disappearance rate of diarrhea—Observational trials |                 |                                             |
| 6 Observational studies                     | 87.5%           | 9 more per 1000 (from 131 fewer to 157 more) |
| No serious risk of bias                     |                 |                                             |
| No serious inconsistency                   |                 |                                             |
| No serious indirectness                    |                 |                                             |
| No serious imprecision                      |                 |                                             |
| None                                       |                 |                                             |
| Plus vs. CPT                                | Control         | Relative (95% CI) Absolute Quality Importance |
| 23/26 (88.5%)                               | 21/24 (87.5%)   | RR 1.01 (0.85 to 1.18) | LOW CRITICAL |
| 9 more per 1000                            | 9 more per 1000  | (from 131 fewer to 157 more) \(\uparrow\) |

(Continues)
| No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of patients | Effect | Quality | Importance |
|---------------|--------|--------------|---------------|--------------|-------------|---------------------|----------------|--------|---------|------------|
|               |        |              |               |              |             |                     | Plus vs.CPT       | Relative (9% CI) | Absolute |           |            |
| Disappearance rate of diarrhea—RCTs |
| 6             | Randomised trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 45/70 (64.3%) | RR 1.09 (0.85 to 1.39) | 55 more per 1000 (from 92 fewer to 259 more) | 76.4% | MODERATE |
|               | Observational trials |
| 3             | Observational studies | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 58/70 (82.9%) | RR 1.15 (0.66 to 1.93) | 97 more per 1000 (from 208 fewer to 604 more) | 61.1% | VERY LOW |
| ALT—RCT |
| 1             | Randomised trials | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | Serious<sup>b</sup> | None | 37/41 (90.2%) | RR 1.28 (1.02 to 1.59) | 198 more per 1000 (from 14 more to 417 more) | 70.7% | LOW |
| AST—Observational trials |
| 3             | Observational studies | Serious<sup>a</sup> | No serious inconsistency | No serious indirectness | No serious imprecision | None | 63/72 (87.5%) | RR 1.25 (0.75 to 2.1) | 167 more per 1000 (from 167 fewer to 733 more) | 57.1% | VERY LOW |
| Quality assessment | No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | No. of patients | Effect | Quality | Importance |
|--------------------|----------------|--------|--------------|---------------|--------------|-------------|---------------------|----------------|--------|---------|------------|
| **AST—RCT**        |                |        |              |               |              |             |                     |                |        |         |            |
| 1                  | Randomised trials | Serious | No serious inconsistency | No serious indirectness | Serious | None |                     | 40/41 (97.6%) | RR 1.21 (1.03 to 1.42) | 169 more per 1000 (from 24 more to 338 more) | CRITICAL | LOW |
|                    |                |        |              |               |              |             |                     | 33/41 (80.5%) | 80.5% |         |            |
| **Aggravation of COVID-19—RCTs** |                |        |              |               |              |             |                     |                |        |         |            |
| 12                 | Randomised trials | Serious | No serious inconsistency | No serious indirectness | No serious imprecision | Strong association | 48/711 (6.8%) | RR 0.46 (0.33 to 0.64) | 81 fewer per 1000 (from 54 fewer to 101 fewer) | IMPORTANT | HIGH |
|                    |                |        |              |               |              |             |                     | 100/664 (15.1%) | 10.1% |         |            |
| **Aggravation of COVID-19—Observational trials** |                |        |              |               |              |             |                     |                |        |         |            |
| 16                 | Observational studies | No serious risk of bias | No serious inconsistency | No serious indirectness | No serious imprecision | Strong association | 52/1300 (4%) | RR 0.4 (0.28 to 0.57) | 77 fewer per 1000 (from 55 fewer to 92 fewer) | IMPORTANT | MODERATE |
|                    |                |        |              |               |              |             |                     | 95/740 (12.8%) | 12.6% |         |            |
| **Time of nucleic acid conversion to negative—RCTs (Better indicated by lower values)** |                |        |              |               |              |             |                     |                |        |         |            |
| 6                  | Randomised trials | Serious | Serious | No serious indirectness | No serious imprecision | Reporting bias | 207 | 216 | MD 3.75 lower (6.19 to 1.3 lower) | IMPORTANT | VERY LOW |

(Continues)
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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