A systematic review of outcomes in COVID-19 patients treated with western medicine in combination with traditional Chinese medicine versus western medicine alone

Ruizhe Yu1,*, Shihan Zhang1,*, Dejian Zhao2,* and Zhanpeng Yuan1,3

1Department of Preventive Medicine, School of Public Health, Wuhan University, Wuhan, Hubei 430071, China; 2Guangdong Provincial Center for Disease Control and Prevention, Guangzhou, Guangdong 511430, China and 3Hubei Provincial Key Laboratory for Applied Toxicology, Wuhan, Hubei 430065, China

Abstract

Background. Since the outbreak of coronavirus disease 2019 (COVID-19) in late 2019, it has evolved into a global pandemic that has become a substantial public health concern. COVID-19 is still causing a large number of deaths in several countries around the world because of the lack of effective treatment.

Aim. To systematically compare the outcomes of COVID-19 patients treated with integrated Chinese with western (ICW) medicine versus western medicine (WM) alone by pooling the data of published literature, and to determine if ICW treatment of COVID-19 patients has better clinical outcomes.

Methods. We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), China Clinical Trial Registry, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Wanfang databases using keywords related to COVID-19, traditional Chinese medicine (TCM) and treatment effect. The search deadline was until 10 February 2021. All randomised controlled (RC) and non-randomised controlled (NRC) clinical trials of the ICW or WM treatment of COVID-19 patients were included. We analysed the effective rate, cure rate, exacerbation rate, turning negative rate of viral nucleic acid, remission rate and remission time of symptoms such as fever, cough, feebleness and chest computed tomography (CT) and the number of white blood cells (WBCs) and lymphocytes (LYM) of the COVID-19 patients. For qualitative and quantitative data, the ratio risk (RR) and weighted mean difference (WMD) were used as the indexes of the statistical analysis, respectively. RevMan 5.4 was used to perform meta-analyses and forest plots with the fixed-effects and random-effects models. Cochrane risk of bias tool (RoB 2.0) was used to assess the risk of bias in the included RC trials, whereas risk of bias in non-randomised studies of interventions was used to assess the risk of bias in NRC trials.

Results. This research includes 16 studies with 1645 valid confirmed COVID-19 patients, among which 895 patients of the experimental group received ICW treatment whereas 750 patients of the control group received WM treatment. The outcomes were assessed in three aspects, that is, overall indicator, symptoms indicator and blood indicator, respectively, and the results showed that the ICW group had better treatment outcomes compared with the WM. Among the overall indicators, the ICW group displayed a higher effective rate (RR = 1.24, 95% confidence interval (CI): 1.16–1.33), clinical cure rate (RR = 1.27, 95% CI: 1.03–1.56) and lower exacerbation rate (RR = 0.36, 95% CI: 0.25–0.52), but no statistical difference was observed in the turning negative rate of viral nucleic acid (RR = 1.20, 95% CI: 0.78–1.85). Among the symptom indicators, the ICW group had a higher fever remission rate (RR = 1.24, 95% CI: 1.09–1.42), less fever remission time (WMD = −1.49, 95% CI: −1.85 to −1.12), a higher cough remission rate (RR = 1.38, 95% CI: 1.10–1.73) and a feebleness remission rate (RR = 1.45, 95% CI: 1.18–1.77), less cough remission time (WMD = −1.61, 95% CI: −2.35 to −0.87) and feebleness remission time (WMD = −1.50, 95% CI: −2.38 to −0.61) and better improvement in chest CT (RR = 1.19, 95% CI: 1.11–1.28). For blood indicator, the number of WBCs in the blood of patients of ICW group rebounded significantly (WMD = 0.35, 95% CI: 0.16–0.54), and the recovery of LYM in the blood was more obvious (WMD = 0.23, 95% CI: 0.06–0.40).

Conclusion. The results of this study show that the outcomes in COVID-19 patients treated by the ICW is better than those treated by the WM treatment alone, suggesting that WM and TCM can be complementary in the treatment of COVID-19.

Introduction

There have been several cases of unexplained pneumonia in hospitals in Wuhan, Hubei province, China, in December 2019. Subsequent research has confirmed that the disease is an acute respiratory infection caused by a new coronavirus infection, which is identified as coronavirus disease 2019 (COVID-19) by the World Health Organization. COVID-19 has caused great harm to the health of people all over the world. As of 5:54 pm CEST on 5 July 2021, there...
had been 183,560,151 confirmed cases of the COVID-19 globally, with 3,978,581 deaths (Ref. 1). Furthermore, it seems that the harm will continue.

Currently, the COVID-19 pandemic in China has been largely contained, but the pandemic is still raging in other countries around the world. Traditional Chinese medicine (TCM), along with western medicine (WM) has contributed greatly to the fight against the pandemic together with WM. Some TCMs such as Jinhua Qinggan granules, Lianhua Qingwen capsules/granules and Xuebijing injection were used to treat COVID-19 patients, and have been proven to be effective. Furthermore, the application rate of TCM among all COVID-19 patients in China is as high as 92% (Ref. 2).

Moreover, some statistical analysis-based studies on the differences between integrated Chinese with western (ICW) and WM in the treatment of COVID-19 have been conducted (Refs 3–7). However, each of the included studies are relatively incomplete with limited indicators analysed. Therefore, the data from ICW with WM and WM-alone treatments for COVID-19 patients from the included literature studies must be pooled to comprehensively compare and evaluate if there is any difference in clinical outcomes among patients. Specifically, our meta-analysis study found that ICW in combination with WM in treating COVID-19 patients obtained better rates of exacerbation reduction, death reduction and cure, and faster recovery compared with those of WM-alone-treated patients. These results imply that ICW joining force with WM in treating COVID-19 patients is a better strategy compared with WM-alone, suggesting the application of ICW actually may have contributed to the relatively quicker containment of the COVID-19 pandemic in China.

Methods

Eligibility criteria

Population: Randomised controlled (RC) and non-randomised controlled (NRC) trials of the patients diagnosed with COVID-19 were included.

Intervention: We included studies, among which the control group received WM treatment and the event group received TCM (including oral medicine and injection) in combination with WM treatment.

Outcomes: To be included, a trial has to have used clinical data of the treatment effects of ICW and WM. We applied no language restrictions. There are no explicit limits on the characteristics of patients such as age, sex, severity of disease and treatment time.

Information sources

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), China Clinical Trial Registry, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI) and Wanfang databases, and the last search date is 10 February 2021.

Search strategy

We searched related articles in the above databases using the following keywords independently or in combination:

(1) COVID-19;
(2) Traditional Chinese Medicine or TCM;
(3) Western Medicine or WM;
(4) Treatment Outcome.

Selection process

Firstly, two researchers (Ruizhe Yu and Dejian Zhao) independently reviewed titles and abstracts of the first 50 records, and discussed inconsistencies until consensus was obtained.

Secondly, two researchers independently screened titles and abstracts of all retrieved articles and reached consensus by discussion.

Finally, two researchers independently screened full-text of the articles, and consensus was also reached on inclusion or exclusion by discussion.

Data extraction process

The two authors extracted data of all indicators from the included articles and recorded them in a data sheet independently. Extracted data were compared, and discrepancies, if any, were resolved through discussion.

Data items

(a) The collected indicators include effective rate, cure rate, exacerbation rate, turning negative rate of viral nucleic acid, remission rate and remission time of symptoms such as fever, cough, feeblesness and chest computed tomography (CT), number of white blood cells (WBCs) and lymphocytes (LYM) of the COVID-19 patients.

(b) We collected data on:
- author, year and source of publication;
- study design, number of patients;
- methods of randomisation, blind or not;
- treatment duration, TCM and WM treatment;
- indicators.

Study risk of bias assessment

We used the revised Cochrane risk of bias tool (RoB 2.0) to assess the risk of bias in the included RC trials. For NRC trials, we used risk of bias in non-randomised studies of interventions (ROBINS-I) to evaluate the risk of bias.

Effect measures

The ratio risk (RR) and weighted mean difference (WMD) were used as the indexes of the statistical analysis for counting data and for continuous data, respectively, and both of which were demonstrated in the above formulas:

\[
RR_i = \frac{a_i/n_{1i}}{c_i/n_{2i}} \text{ with standard error } se[\ln (RR_i)] = \sqrt{1/a_i} + 1/c_i - 1/n_{1i} - 1/n_{2i}
\]

where \(a_i\) and \(c_i\) are the events, and \(n_{1i}\) and \(n_{2i}\) are the group size for two studied groups in study \(i\), respectively.

\[
WMD_i = m_{1i} - m_{2i} \text{ with standard error } se(WMD_i) = \sqrt{sd_{1i}^2/n_{1i} + sd_{2i}^2/n_{2i}}
\]

where \(m_{1i}\) and \(m_{2i}\) are the mean response, \(sd_{1i}\) and \(sd_{2i}\) are the standard deviations for the two studied groups in study \(i\), respectively.

Synthesis methods

RevMan 5.4 software provided by the Cochrane Collaboration was used for the meta-analysis. We used forest plot to present study
results, and subgroup analysis was used because of the difference in data quality of RC and NRC trials.

Heterogeneity of all studies was evaluated through the $I^2$ test. When $P \geq 0.1$ and $I^2 \leq 50\%$, the fixed-effects model is used considering the small heterogeneity. When $P < 0.1$ and $I^2 > 50\%$, the random-effects model is used considering the large heterogeneity; we analysed the source of heterogeneity and conducted a subgroup analysis based on the possible heterogeneity factors.

Moreover, sensitivity analysis was used to analyse stability of the test results. When the heterogeneity was so large that the source cannot be judged, we analysed the data by using descriptive analysis rather than meta-analysis.

### Reporting bias assessment

Publication bias by the funnel plot was evaluated if the number of studies included in the meta-analysis reached 10. If the points on the funnel plot were scattered symmetrically and showed an inverted symmetrical funnel shape, it indicated that the publication bias of the included study was small, and if the points on the funnel plot were clustered, the publication bias was considered large.

### Results

#### Study selection

A total of 331 records were found in databases, including 42 English articles and 289 Chinese articles. After manual removal of duplicates, 299 records were retained. We screened titles and abstracts of 299 records, from which we reviewed 21 full-text documents of the included records. Finally, 16 articles were included. Figure 1 shows the flow diagram of study selection.

#### Study characteristics

The 16 included studies contained 1649 patients with confirmed COVID-19 status, and the general characteristics assessed were author, study design, number of patients, methods of randomisation, blind or not, treatment duration, TCM and WM treatment and indicators, as shown in Table 1.

The indicators are divided into three categories, that is, overall indicator, symptom indicator and blood indicator. The overall indicators include effective rate (numbered as ① in Table 1), turning negative rate of viral nucleic acid (numbered as ②), exacerbation rate (numbered as ③) and cure rate (numbered as ④). The symptom indicators include fever remission rate or time (numbered as ⑤), cough remission rate or time (numbered as ⑥), sputum disappearance rate or time (numbered as ⑦) and chest CT improvement rate (numbered as ⑧). The blood indicators include WBC amounts (numbered as ⑨) and LYM amounts (numbered as ⑩).

#### Risk of bias in studies

Among the 16 studies assessed, seven studies were RC trials, and the rest were NRC trials, which included 10 trials in the remaining nine studies.

For RC trials, risk of bias assessment (RoB2) (Ref. 24) recommended by Cochrane was used. Because of sudden outbreak of the epidemic, allocation of intervention measures was mainly based on medical humanity, and patient health along with baseline data of the patients were basically the same, so it did not interfere with the research conclusions. Except in the study by Ding et al. (Ref. 10), where the investigators did not mention the use of a reasonable scale when measuring the patient's fever, cough and other symptoms, appropriate measuring methods were used in all the other studies. All of the studies provided complete outcome data, and none of them reported results selectively. Moderate quality results among these RC trials are shown in Figure 2a and b.

The ROBINS-I (Ref. 25) was used to evaluate NRC trials. Most NRC trials have issues associated with baseline confounding and only Chen (Ref. 8) and Cheng (Ref. 9) have used effective and reliable methods of propensity matching and comparability analysis of baseline data. Moreover, no time-varying confounding problem was observed in the included studies. The time of admission and the time point at which intervention began differed, but the intervention effect was only affected by the duration of intervention, so the risk of bias among the subjects was moderate. All research interventions were well-defined, and there were no interfering factors other than the interventions used in the control group and the event group. All data were fully reported. We maintained a unified standard for the outcome evaluation method between the intervention groups, and there was no selective reporting of the results. Therefore, overall risk of bias is moderate, and detailed results about risk of bias are shown in Table 2.

#### Results of individual studies and syntheses

##### Overall indicator

**Effective rate:** The ‘effective rate’ is derived from the curative effect criterion which is divided into three levels: significantly effective, effective and ineffective with a detailed explanation as follows.

- **Significantly effective:** Chinese medical symptoms and signs disappeared or significantly reduced, and the total score was reduced by $\geq 70\%$ and (2) **Effective:** Chinese medical symptoms and signs were reduced, with $30\% \leq$ total score reduction $< 70\%$ and (3) **Ineffective:** Chinese medical symptoms and signs did not improve, and the total score was reduced by $< 30\%$ (Ref. 26).

Seven studies reported effective rate indicators. We used subgroup analysis because of the differences between the data qualities of RC and NRC trials. A fixed-effects model was used owing to the minor heterogeneity. The meta-analysis showed that the effective rate of the ICW group was significantly higher than that of the pure WM group. The indicators obtained were $RR = 1.24$, $95\% CI: 1.16\text{–}1.33$ and $P < 0.01$, and is shown in Figure 3. Publication bias was not performed because of the limited number of studies. The results of meta-analysis did not change after excluding each study separately through sensitivity analysis.

**Cure rate:** The definition of ‘clinical cure rate’ is based on the ‘New Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Sixth Edition)’ (Ref. 27). The criteria are as follows: (1) body temperature returns to normal for more than 3 days and (2) respiratory symptoms improve significantly, and obvious absorption of inflammation is shown on the chest CT at least twice and (3) a negative for COVID-19 viral nucleic acid.

Three studies reported cure rate data. We used subgroup analysis because of the differences between the data qualities of RC and NRC trials. A fixed-effects model was used owing to the minor heterogeneity. The meta-analysis results indicated that the cure rate of ICW group is better than that of the WM group. The indicators observed were $RR = 1.27$, $95\% CI: 1.03\text{–}1.56$, $P < 0.02$, and is shown in Figure 4. Publication bias was not performed because of the limited number of studies. The sensitivity analysis of cure rate was not carried out because only three studies involved cure rate and excluding any one of the three studies will seriously affect the results of meta-analysis.

**Exacerbation rate:** Seven trials reported the rate of exacerbation. We used subgroup analysis because of the differences...
Fig. 1. Flow diagram of literature selection.

Note: * indicates the following databases: PubMed, Embase, CETRAL, China Clinical Trial Registry, CBM, CNKI and Wanfang

| Study ID   | Study design | No. of patients | Methods of randomisation | Blind | Treatment duration (days) | TCM                          | WM                          | Indicators |
|------------|--------------|-----------------|--------------------------|-------|---------------------------|------------------------------|------------------------------|------------|
| Chen (Ref. 8) | NRC          | 115/115         | No                       | NR    | 7                         | Ganlu Xiaodu decoction      | Arbidol                     | ①③⑤⑥⑦⑧⑨⑩ |
| Cheng (Ref. 9) | NRC          | 51/51           | No                       | NR    | 7                         | Lianhua Qingwen capsules    | Antiviral drugs              | ①③⑤⑥⑦   |
| Ding (Ref. 10) | RC           | 51/49           | Computer list            | NR    | 10                        | Qingfei Toujie Fuzheng recipe | Antiviral drugs              | ⑤⑥⑧   |
| Duan (Ref. 11) | RC           | 82/41           | Computer list            | NR    | 5                         | Jinhu Qinggan granules      | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Fu (Ref. 12) | RC           | 37/36           | NR                       | NR    | NR                        | Toujie Quwen granules       | Arbidol                     | ⑤⑥⑧⑨⑩⑪ |
| Fu (Ref. 13) | RC           | 32/33           | Random table             | NR    | 10                        | Toujie Quwen granules       | Arbidol                     | ⑤⑥⑧⑨⑩⑪ |
| Huang_1 (Ref. 14) | NRC         | 30/15           | No                       | NR    | NR                        | Other combinations          | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Huang_2** (Ref. 14) | NRC         | 28/15           | No                       | NR    | NR                        | Other combinations          | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Li (Ref. 15) | NRC          | 30/30           | No                       | NR    | NR                        | Qingfei Paidu decoction     | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Qu (Ref. 16) | NRC          | 40/30           | No                       | NR    | 10                        | Shufeng Jiedu capsules      | Arbidol                     | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Shi (Ref. 17) | NRC          | 49/18           | No                       | NR    | NR                        | Other combinations          | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Xia (Ref. 18) | NRC          | 34/18           | No                       | NR    | NR                        | Other combinations          | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Xiao (Ref. 19) | RC           | 100/100         | NR                       | NR    | 14                        | Shufeng Jiedu capsules      | Arbidol                     | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Yang (Ref. 20) | RC           | 26/23           | NR                       | NR    | 7                         | Reyanning mixture           | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Yao (Ref. 21) | NRC          | 21/21           | No                       | NR    | NR                        | Lianhua Qingwen granules    | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Yu (Ref. 22)  | RC           | 147/148         | Random table             | NR    | 7                         | Lianhua Qingwen granules    | Arbidol                     | ③④⑤⑥⑦⑧⑨⑩⑪ |
| Zhang (Ref. 23) | NRC          | 22/22           | No                       | NR    | 7                         | Xuebijing injection         | Antiviral drugs              | ③④⑤⑥⑦⑧⑨⑩⑪ |

NR denotes that the characteristic is not reported. The symbol ‘**’ denotes that there are two trials in the study of Huang.
between the data qualities of RC and NRC trials. A fixed-effects model was used owing to the minor heterogeneity.

The findings indicated that the addition of TCM effectively slows the progression of the disease and improves its symptoms. Therefore, the exacerbation rate of ICW treatment was significantly lower than that of pure WM treatment, and the meta-analysis was observed to be statistically significant. The corresponding indicators obtained were RR = 0.36, 95% CI: 0.25–0.52, \( P < 0.01 \), and is shown in Figure 5. Publication bias was not performed because of the limited number of studies. The result of meta-analysis did not change after excluding each study separately through sensitivity analysis.

![Fig. 2. (a) Risk of bias graph of seven RC trials. (b) Risk of bias summary of seven RC trials.](image)

**Table 2.** Risk of bias evaluation on 10 NRC trials in nine studies

| Study | Bias because of confounding | Bias in selection of participants into study | Bias in classification of interventions | Bias because of deviations from intended interventions | Bias because of missing data | Bias in measurement of outcomes | Bias in selection of reported result | Overall bias |
|-------|-----------------------------|---------------------------------------------|----------------------------------------|------------------------------------------------------|-----------------------------|----------------------------------|------------------------------------|-------------|
| Chen (Ref. 8) | Low | Moderate | Low | Low | Low | Low | Low | Moderate |
| Cheng (Ref. 9) | Low | Moderate | Low | Low | Low | Low | Low | Moderate |
| Huang_1 (Ref. 14) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Huang_2** (Ref. 14) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Li (Ref. 15) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Qu (Ref. 16) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Shi (Ref. 17) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Xia (Ref. 18) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Yao (Ref. 21) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Zhang (Ref. 23) | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |

The symbol **"** denotes that there are two trials in the study of Huang.
Turning negative rate of viral nucleic acid: Only three studies reported the turning negative rate of viral nucleic acid. We used subgroup analysis because of the differences in the data qualities between the RC and NRC trials. The subgroup analysis results indicated that the study design may be the source of heterogeneity. The random-effects model was adopted because of the high heterogeneity.

No statistically significant difference of the viral nucleic acid turning negative rate was observed between the treatment of ICW and that of WM. The corresponding indicators obtained were RR = 1.20, 95% CI: 0.78–1.85, P = 0.41, and is shown in Figure 6. Publication bias was not performed because of the limited number of studies. Sensitivity analysis of cure rate was not carried out because only three studies involved cure rate and excluding any one of the three studies will seriously affect the results of meta-analysis.

Symptom indicator

Fever remission rate: Five studies reported the fever remission rate. We used subgroup analysis because of the difference between the data qualities between RC and NRC trials. The subgroup analysis results indicated that the study design may be the source of heterogeneity. The random-effects model was adopted because of the high heterogeneity.

The result of meta-analysis showed that the fever remission rate of the ICW treatment was better than that of the WM treatment statistically. The indicators of meta-analysis on fever remission rate were RR = 1.24, 95% CI: 1.09–1.42, P = 0.001, and is shown in Figure 7. Publication bias was not performed because of the limited number of studies. The result of meta-analysis did not change after excluding each study separately through sensitivity analysis.

Fever remission time: Eight trials reported the fever remission time. We used subgroup analysis because of the differences...
between the data qualities of RC and NRC trials. The subgroup analysis results indicated that the study design may be the source of heterogeneity. Among these eight trials, only Xiao et al. (Ref. 19) used RC design whereas other studies used NRC studies. The random-effects model was adopted because of the high heterogeneity.

The results of meta-analysis showed that the fever remission time of the ICW treatment was obviously statistically better than that of WM treatment. The indicators of meta-analysis on fever remission time were WMD = −1.49, 95% CI: −1.85 to −1.12, P < 0.01 and are shown in Figure 8. Publication bias was not performed because of the limited number of studies. The result of meta-analysis did not change after excluding each study separately through sensitivity analysis.

Cough remission rate: Five studies reported the cough remission rate. We used subgroup analysis because of the differences between the data qualities of RC and NRC trials. The subgroup analysis results indicated that the study design may be the source of heterogeneity. The random-effects model was adopted considering the large heterogeneity.

The results from the meta-analysis showed that the cough remission rate of ICW treatment was statistically better than that of WM treatment. The indicators of meta-analysis on cough remission rate were RR = 1.38, 95% CI: 1.10–1.73, P = 0.005, and are shown in Figure 9. Publication bias was not performed because of the limited number of studies. The result of meta-analysis did not change after excluding each study separately through sensitivity analysis.
source of heterogeneity. The random-effects model was adopted because of the large heterogeneity from the study by Xiao et al. (Ref. 19).

The results of meta-analysis showed that the cough remission time of ICW treatment was statistically less than that of WM treatment. The indicators of meta-analysis on cough remission time were WMD = -1.61, 95% CI: -2.35 to -0.87, P < 0.0001, and is shown in Figure 10. Publication bias was not performed because of the limited number of studies. Meta-analysis results did not change after excluding each study separately through sensitivity analysis.

**Feebleness remission rate:** Five trials reported feebleness remission time. We used subgroup analysis because of the differences between the data qualities of RC and NRC trials. The subgroup analysis results indicated that the study design may be the source of heterogeneity. The random-effects model was adopted because of the large heterogeneity from the study by Xiao et al. (Ref. 19).

The meta-analysis results showed that the feebleness remission rate of ICW treatment was statistically better than that of WM treatment. The indicators of meta-analysis on feebleness remission rate were RR = 1.45, 95% CI: 1.18–1.77, P < 0.01, and is shown in Figure 11. Publication bias was not performed because of the limited number of studies. Meta-analysis results did not change after excluding each study separately through sensitivity analysis.

**Feebleness remission time:** Five trials reported feebleness remission time. We used subgroup analysis because of the differences between the data qualities of RC and NRC trials. The subgroup analysis results indicated that the study design may be the source of heterogeneity. The random-effects model was adopted because of the large heterogeneity from the study by Xiao et al. (Ref. 19).

The meta-analysis results showed that the feebleness remission time of ICW treatment is statistically less than that of the WM treatment. The indicators of meta-analysis on feebleness remission time were identified as WMD = -1.50, 95% CI: -2.38 to -0.61, P < 0.001, and is shown in Figure 12. Publication bias was not performed because of the limited number of studies.
Meta-analysis results did not change after excluding each study separately through sensitivity analysis.

Chest CT improvement rate: CT evaluation criteria (Ref. 28) were established to assess treatment efficacy. It is characterised as lesion absorption when reduction of lesion area \( \geq 70\% \), and as improved when reduction of lesion area \( \geq 30\% \). If there is no change in the lesion area it is characterised as no change. When the increase of lesion area is \( >30\% \), it is characterised as aggravated. The lesion absorption and improvement are effective.

Ten trials reported chest CT improvement rate. We used subgroup analysis because of the differences between the data qualities of RC and NRC trials. The fixed-effects model was used owing to the minor heterogeneity.

Obviously, meta-analysis results indicated that the chest CT of ICW treatment was significantly higher than that of the WM treatment. The indicators obtained were RR = 1.19, 95% CI: 1.11–1.28, \( P < 0.001 \), and is shown in Figure 13. We assessed the potential publication bias by using funnel plots. It showed no significant publication bias among the included studies as shown in Figure 14. The result of meta-analysis did not change after excluding each study separately through sensitivity analysis.

Blood indicator
Comparability of WBC and LYM before treatment: The guidelines state that patients with COVID-19 may experience a decrease in WBC and LYM. If the patient’s LYM is significantly reduced, the patient is prompted to have a poor prognostication, which will have a high risk of heavy exacerbation (Ref. 29). We compared the pre-treatment WBC and LYM data to prove the comparable baseline.
data of WBCs. The indicators obtained were WMD = −0.07, 95% CI: −0.14 to 0.00, P = 0.06, and is shown in Figure 15. Publication bias was not performed because of the limited number of studies. The result of meta-analysis did not change after excluding each of studies separately through sensitivity analysis.

For the LYM count, five studies described the pre-treatment data of LYM. We used subgroup analysis because of the differences between the data qualities of RC and NRC trials. The random-effects model was adopted because of the major heterogeneity between the studies and the study by Yu et al. (Ref. 22). Meta-analysis results suggested that there were no statistical differences among LYM pre-treatment data. The indicators obtained were WMD = 0.02, 95% CI: −0.03 to 0.08, P = 0.38, and is shown in Figure 16. Publication bias was not performed because of the limited number of studies. The result of meta-analysis changed after excluding the study by Yu et al. (Ref. 22) separately through sensitivity analysis.

WBC and LYM after treatment: We compared the after-treatment data of WBCs and LYM to prove the effect of the treatment. Meta-analysis indicates that the ICW group is better than the WM group in improving immunity and reducing the risk of inflammation.

For the five studies that reported the WBC count after treatment, we used subgroup analysis because of the differences between the data qualities of RC and NRC trials. The random-effects model was adopted because of the large heterogeneity. The indicators obtained were WMD = 0.35, 95% CI: 0.16–0.54, P < 0.001, and is shown in Figure 17. Publication bias was not performed because of the limited number of studies. The result of meta-analysis did not change after excluding each study separately through sensitivity analysis.

For the five studies that reported the LYM count after treatment, we used subgroup analysis because of the differences between the data qualities of RC and NRC trials. The random-effects model was adopted because of the large heterogeneity. The indicators obtained were WMD = 0.23, 95% CI: 0.06–0.40, P = 0.008, and is shown in Figure 18. Publication bias was not performed because of the limited number of studies. The result of meta-analysis changed after excluding the study by Fu et al. (Ref. 13) separately through sensitivity analysis.
COVID-19, an extremely contagious disease, is caused by a previously unknown type of coronavirus. Because of our limited knowledge about the disease at the beginning of the outbreak, we remained at the exploratory stage of treatment plan. However, there were several retrospective analyses, resulting in several low-quality studies. However, it has become evident that ICW is helpful in improving the symptoms among patients with mild-to-moderate symptoms.

Based on previous experiences, the combination of Chinese and WMs can usually complement each other and achieve good results. For example, some adverse events related to the use of corticosteroids, for example, fungal infections, have made corticosteroids controversial in the treatment of severe acute respiratory syndrome (SARS) patients (Refs 30, 31). There are reports which indicate that some SARS survivors who received high-dose corticosteroids developed femoral head necrosis after treatment (Refs 32, 33). According to evidence-based medicine report, the application of Chinese
medicine can be helpful to effectively reduce the daily average use dose of corticosteroids (Ref. 34). In the Guangdong Provincial Hospital of Traditional Chinese Medicine, Chinese medicine is used as the primary treatment for the early, middle, extreme and convalescent periods of the SARS disease even without the use of corticosteroids and antiviral drugs, thus indicating that it is feasible and safe to treat patients with TCM-alone (Ref. 35).
With SARS-CoV-2 infection, 20% of patients will rapidly develop severe disease manifestations including atypical interstitial pneumonia, acute respiratory distress syndrome and multiple organ dysfunctions, and nearly 10% among will die eventually. It is fortunate that the pathological mechanism of this disease evolution is being revealed gradually. Studies show that excessive immune response characterised as extensive endothelial damage, complement-induced blood coagulation and systemic microvascular disease plays a key role in disease progression (Ref. 36). By observing histopathological changes in lungs, spleen, liver, heart, kidney, thyroid and testis of patients who died because of COVID-19, it was found that the patient’s high-inflammation and repair states coexisted, and the high-inflammation state caused pathological processes such as coagulation status, microthrombosis, fibrosis and angiogenesis (Ref. 37). Therefore, it is necessary to start early treatment procedures for patients with severe disease symptoms to prevent multiple organ fibrosis. In the previous application of the ICW, 36 kinds of Chinese medicine monomer active ingredients such as baicalein (Refs 38, 39), puerarin (Ref. 40), gallic acid (Refs 41, 42) and astragaloside (Ref. 43) and other 25 kinds of Chinese medicinal compound active ingredients such as Yupingfeng powder (Refs 44–46), Bufei decoction (Refs 47, 48) and Buyang Huanwu decoction (Ref. 49) were used, and these medicinal compounds can reduce the expression of inflammatory factors and regulate the balance of redox, induce apoptosis of lung fibroblasts and block the process of fibrosis through the transforming growth factor-β1/Smad, phosphatidylinositol-3-kinase/Akt and nuclear erythroid 2-related factor 2/glutathione or other pathways, which indicates good anti-pulmonary fibrosis activity and can effectively improve symptoms of fibrosis and delay disease progression (Refs 50, 51). This may explain why the ICW treatment has better therapeutic effect compared with WM treatment. Therefore, TCM, especially the compound prescriptions, have a good prospect for the clinical application in prevention and treatment of fibrosis (Ref. 52), but more related clinical trials should be carried out to cope with moderate and severe patients of COVID-19.

**Conclusion**

Treatment experiences from previous emerging contagious diseases, such as SARS and H1N1, have proven that the ICW treatment has better treatment outcomes than mere WM treatment, and this study has come to a similar conclusion. Pooled 16 studies were systematically analysed for differences between the ICW and WM treatments in three broad categories, that is, overall indicators, symptom indicators and blood indicators by meta-analysis. The results showed that the combination of Chinese medicine played a significant role in better controlling the exacerbation of patient’s condition, improving cure rate and repairing immunity of COVID-19 patients.

The treatment experiences of SARS, H1N1 and COVID-19 all have shown that Chinese medicine has complementary effects with WM. All these seem to suggest that Chinese medicine could withstand the challenge of fighting emerging epidemic diseases. Thus, it is valuable to carry out more such practices and further research, which would facilitate the development of Chinese medicine and perhaps benefit the world. It is, therefore, reasonable to speculate that Chinese medicine, and perhaps other traditional medicine, can aid in our fighting against emerging epidemic diseases in the future.

**Financial support.** This research received no external funding.

**Conflict of interest.** The authors declare no conflict of interest.

**References**

1. World Health Organization. Coronavirus Disease (COVID-19) Dashboard. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
2. The State Council Information Office of the People’s Republic of China. Fighting COVID-19: China in Action. June 2020. Available at http://www.scio.gov.cn/zbds/32932/Document/1681809/1681809.htm.
3. Zhou F et al. (2021) Efficacy and safety of Chinese herbal decoction combined with western medicine in treatment of COVID-19: a meta-analysis. Journal of Medical 37, 564–568.
4. Fan A et al. (2020) Chinese herbal medicine for COVID-19: current evidence with systematic review and meta-analysis. Journal of Integrative Medicine 18, 385–394.
5. Liu L et al. (2021) A review and meta-analysis of clinical efficacy and safety of the integrative medicine on COVID-19. Clinical Journal of Chinese Medicine 13, 24–30.
6. Cai X et al. (2020) Meta-analysis of the combination of the traditional Chinese and western medicine in the treatment of COVID-19. Journal of Baotou Medical College 36, 95–98.
7. Ouyang J et al. (2021) Efficacy and safety of traditional Chinese medicine for patients with mild or common COVID-19: a meta-analysis. Journal of Traditional Chinese Medical Sciences 30, 17–20 + 26.
8. Chen L et al. (2020) Retrospective analysis on clinical efficacy of Ganlu Xiaodu decoction combined with western medicine in treatment of common COVID-19 patients. Chinese Journal of Experimental Traditional Medical Formulae 26, 60–67.

Downloaded from https://www.cambridge.org/core. IP address: 207.241.231.108, on 28 Jan 2022 at 00:28:49, subject to the Cambridge Core terms of use, available at https://www.cambridge.org/core/terms. https://doi.org/10.1017/erm.2021.35
9. Cheng D et al. (2020) Analysis of curative effect of 51 patients with novel coronavirus pneumonia treated with Chinese medicine Lianhu Qingwen: a multicentre retrospective study. Tianjin Journal of Traditional Chinese Medicine 37, 509–516.

10. Ding X et al. (2020) Clinical effect and mechanism of Qingfei Touxie Fuzheng recipe in the treatment of COVID-19. Herald of Med 39, 640–644.

11. Duan C et al. (2020) Clinical observation on Jinhua Qinqgan granule combined with conventional western medicine therapy in treating mild cases of coronavirus disease 2019. Journal of Traditional Chinese Medicine 61, 1473–1477.

12. Fu X et al. (2020) Clinical study on 37 case of COVID-19 treated with integrated traditional Chinese and western medicine. Traditional Chinese Drug Research & Clinical Pharmacology 31, 600–604.

13. Fu X et al. (2020) Clinical observation on effect of Toujie Qwen granules in treatment of COVID-19. Chinese Journal of Experimental Traditional Medical Formulae 26, 44–48.

14. Huang H et al. (2020) Analysis of traditional Chinese medical syndrome and clinical efficacy of 72 patients with COVID-19. Modern Journal of Integrated Traditional Chinese and Western Medicine 29, 2395–2399 + 2483.

15. Li K et al. (2020) Observation on clinical effect of modified Qingfei Paud decoction in treatment of COVID-19. Chinese Traditional and Herbal Drugs 51, 1167–1170.

16. Qiu X et al. (2020) Observation on clinical effect of Shufeng Jiedu capsule combined with arbidol hydrochloride capsule in treatment of COVID-19. Chinese Traditional and Herbal Drugs 51, 1167–1170.

17. Shi J et al. (2020) Clinical observation on 49 cases of non-critical COVID-19 in Shanghai treated by integrated traditional Chinese and western medicine. Shanghai Journal of Traditional Chinese Medicine 54, 30–35.

18. Xia W et al. (2020) Clinical observation on 34 patients with novel coronavirus pneumonia (COVID-19) treated with integrated traditional Chinese and western medicine. Journal of Traditional Chinese Medicine 61, 375–382.

19. Xiao Q et al. (2020) Analysis of the value of traditional Chinese medicine Shufeng Jiedu capsules combined with arbidol in the treatment of mild COVID-19. Journal of Traditional Chinese Medical Sciences 29, 756–758.

20. Yang M et al. (2020) Multi-center clinical observation of Reyanning mixture in treatment of COVID-19. Chinese Journal of Experimental Traditional Medical Formulae 26, 7–12.

21. Yao K et al. (2020) Retrospective clinical analysis on treatment of coronavirus disease 2019 with traditional Chinese medicine Lianhu Qingwen. Chinese Journal of Experimental Traditional Medical Formulae 26, 8–12.

22. Yu P et al. (2020) Efficacy of Lianhu Qingwen granules combined with arbidol in the treatment of mild COVID-19. Chinese Pharmacetical Journal 55, 1042–1045.

23. Zhang C et al. (2020) Clinical observation of Xuebijingin the treatment of COVID-19. Chinese Journal of Hospital Pharmacy 40, 964–967.

24. Sterne JAC et al. (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366, 14898.

25. Sterne JA et al. (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919.

26. State Administration of Medicines and Food Supervision and Administration. Guidelines for Clinical Research of new Chinese Medicines (revised in 2010) [M]. Beijing: China Medical Science and Technology Press.

27. National Health Commission, State Administration of Traditional Chinese Medicine. New Coronavirus Pneumonia diagnosis and treatment plan (Trial Sixth Edition). [EB/OL]. Available at http://www.gov.cn/zhengce/zhengcecout/2020-02/19/content_5480948.htm/2020-02-18/2020-02-26.

28. Infection and Inflammation Radiology Professional Committee of Chinese Research Hospital Association (2020) Guidelines for imaging aided diagnosis of new coronavirus pneumonia. Chinese Journal of Medical Imaging Technology 3, 321–331.

29. Huang C et al. (2020) Clinical features of patients infected with 2019 novel coronavirus. In: W. Chan, L. Lai, Eds. Lancet (London, England) 395, 497–506.

30. Griffith JF et al. (2005) Osteonecrosis of hip and knee in patients with severe acute respiratory syndrome treated with steroids. Radiology 235, 168–175.

31. Wang H et al. (2003) Fatal Aspergillosis in a patient with SARS who was treated with corticosteroids. New England Journal of Medicine 349, 507–508.

32. Hong N et al. (2005) Diffusion-weighted MR study of femoral head avascular necrosis in severe acute respiratory syndrome patients. Journal of Magnetic Resonance Imaging: JMRI 22, 661–664.

33. Shen J et al. (2004) Report on the investigation of lower extremity osteonecrosis with magnetic resonance imaging in recovered severe acute respiratory syndrome in Guangzhou. National Medical Journal of China 84, 1814–1817.

34. Chen Y et al. (2007) Effect of integrated traditional Chinese medicine and western medicine on the treatment of severe acute respiratory syndrome: a meta-analysis. Journal of Pharmacy Practice 5, 1–9.

35. He D et al. (2004) Treatment of SARS mainly by Chinese herbal drugs: a clinical observation of 34 cases. New Chinese Medicine 12, 20–21.

36. Perico L et al. (2021) Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nature Reviews. Nephrology 17, 46–64.

37. Nie X et al. (2021) Multi-organ proteomic landscape of COVID-19 autopsies. Cell 184, 775–791.

38. Cui X et al. (2018) Baiacalein represses TGF-β1-induced fibroblast differentiation through the inhibition ofmr-21. Toxicology and Applied Pharmacology 358, 35–42.

39. Sun X et al. (2020) Baiacalein alleviated TGF-β1-induced type I collagen production in lung fibroblasts via downregulation of connective tissue growth factor. Biomedeicne & Pharmacotherapy 131, 110744.

40. Hu X and Huang X (2019) Alleviation of inflammatory response of pulmonary fibrosis in acute respiratory distress syndrome by puerarin via transforming growth factor (TGF-β1). Medical Science Monitor: International Medical Journal of Experimental and Clinical Research 25, 6523–6531.

41. Jin L et al. (2017) Gallic acid attenuates pulmonary fibrosis in a mouse model of transverse aortic constriction-induced heart failure. Vascular Pharmacology 99, 74–82.

42. Rong Y et al. (2018) A novel gallic acid derivative attenuates BLM-induced pulmonary fibrosis in mice. International Immunopharmacology 64, 183–191.

43. Cho I et al. (2015) Astragalus inhibits autophagy-associated airway epithelial fibrosis. Respiratory Research 16, 51.

44. Xu L et al. (2014) Total polysaccharide of Yupingfeong protects against bleomycin-induced pulmonary fibrosis via inhibiting transforming growth factor-β1-mediated type I collagen abnormal deposition in rats. Journal of Pharmacy and Pharmacology 66, 1786–1795.

45. Li L et al. (2015) Total extract of Yupingfeong attenuates bleomycin-induced pulmonary fibrosis in rats. Phytomedical: International Journal of Phytophathology and Phytopharmacology 22, 111–119.

46. Cui W et al. (2015) Total glycosides of Yupingfeong protects against bleomycin-induced pulmonary fibrosis in rats associated with reduced high mobility group box1 activation and epithelial-mesenchymal transi- tion. Inflammation Research 64, 953–961.

47. Yang J et al. (2010) Experimental study on effect of Bufei decoction on TGF-β1 expression in lung tissue of rats with pulmonary fibrosis. Chinese Journal of Traditional Medical Science and Technology 17, 291–292, 303, 280.

48. Zhang H et al. (2011) Study on effects of Bufei decoction on MMP-9 and TIMP-1 in lung tissue of pulmonary fibrosis rats. Archives of Traditional Chinese Medicine 29, 2673–2679.

49. Wang X et al. (2018) Buyang Huanwu decoction ameliorates bleomycin-induced pulmonary fibrosis in rats via downregulation of related protein and gene expression. Evidence-Based Complementary and Alternative Medicine: ECAM 2018, 9185485.

50. Ding D et al. (2021) Research progress of traditional Chinese medicine in treating pulmonary fibrosis. Chinese Traditional and Herbal Drugs 1–19. doi: http://kns.cnki.net/kcms/detail/12.1108.R.20210421.1427.002.html.

51. Leung E et al. (2020) The scientific foundation of Chinese herbal medi- cine against COVID-19. Engineering (Beijing) 6, 1099–1107.

52. Ma L et al. (2020) Analysis of the law of traditional Chinese medicine for the treatment of pulmonary fibrosis based on data mining. Chinese Traditional and Herbal Drugs 51, 1406–1411.