Chinese Medical Journal®

Comparative effectiveness and safety of 32 pharmacological interventions recommended by guidelines for coronavirus disease 2019: a systematic review and network meta-analysis combining 66 trials

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Abstract

Background: The global pandemic coronavirus disease 2019 (COVID-19) has become a major public health problem and presents an unprecedented challenge. However, no specific drugs were currently proven. This study aimed to evaluate the comparative efficacy and safety of pharmacological interventions in patients with COVID-19.

Methods: Medline, Embase, the Cochrane Library, and clinicaltrials.gov were searched for randomized controlled trials (RCTs) in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/SARS-CoV. Random-effects network meta-analysis within the Bayesian framework was performed, followed by the Grading of Recommendations Assessment, Development, and Evaluation system assessing the quality of evidence. The primary outcome of interest includes mortality, cure, viral negative conversion, and overall adverse events (OAEs). Odds ratio (OR) with 95% confidence interval (CI) was calculated as the measure of effect size.

Results: Sixty-six RCTs with 19,095 patients were included, involving standard of care (SOC), eight different antiviral agents, six different antibiotics, high and low dose chloroquine (CQ_HD, CQ_LD), traditional Chinese medicine (TCM), corticosteroids (COR), and other treatments. Compared with SOC, a significant reduction of mortality was observed for TCM (OR = 0.34, 95% CI: 0.20–0.56, moderate quality) and COR (OR = 0.84, 95% CI: 0.75–0.96, low quality) with improved cure rate (OR = 2.16, 95% CI: 1.60–2.91, low quality for TCM; OR = 1.17, 95% CI: 1.05–1.30, low quality for COR). However, an increased risk of mortality was found for CQ_HD *vs.* SOC (OR = 3.20, 95% CI: 1.18–8.73, low quality). TCM was associated with decreased risk of OAE (OR = 0.52, 95% CI: 0.38–0.70, very low quality) but CQ_HD (OR = 2.51, 95% CI: 1.20–5.24) and interferons (IFN) (OR = 2.69, 95% CI: 1.02–7.08) *vs.* SOC with very low quality were associated with an increased risk.

Conclusions: COR and TCM may reduce mortality and increase cure rate with no increased risk of OAEs compared with standard care. CQ_HD might increase the risk of mortality. CQ, IFN, and other antiviral agents could increase the risk of OAEs. The current evidence is generally uncertain with low-quality and further high-quality trials are needed.

Keywords: SARS-CoV-2; COVID-19; Pharmacological intervention; Network meta-analysis; Effectiveness; Safety

Introduction

As of June 15, 2021, more than 175.8 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has similar genetics to SARS-CoV.[1] This global pandemic coronavirus disease 2019 (COVID-19) has caused 859,130 deaths in 216 countries, which has become a major public health problem and presents an unprecedented challenge.[1]

So far, many kinds of drugs in addition to standard of care (SOC) are recommended by different clinical guide-

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001672

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Chinese Medical Journal 2021;134(16)
Received: 29-04-2021 **Edited by:** Jing Ni

lines,[2-5] including antiviral agents, immune-based therapies (such as corticosteroids [COR], convalescent plasma [CON_PLA], and interferons [IFN]), hydroxychloroquine or chloroquine (CQ), traditional Chinese medicine (TCM), and other adjunctive therapies. However, no specific drugs were currently proven and nearly all drugs are off-label prescribed.[6] Despite numerous ongoing or finished clinical trials, substantial uncertainty about effectiveness and safety still exists in these therapies owing to limited sample size and large variability with insufficient power.

Although several meta-analyses have been available,[7-13] most are pairwise comparisons between two kinds of drugs with few studies included or only narrative synthesis. Moreover, methodological limitations exist in most meta-analyses, such as combining observational studies with randomized controlled trials (RCTs), mistaking cohort studies as RCTs, mixing controlled groups, and omitting searching Chinese databases.[14-17] Additionally, these pairwise meta-analyses are not able to provide evidence on the comparative effectiveness and safety of all available treatments. While several network meta-analyses (NMA) are ongoing,[18-20] no results for the comprehensive assessment have been reported, and some treatments such as TCM and blood products are not included in these NMA. Furthermore, their network is sparse without the inclusion of similar genetic SARS-CoV studies. Besides, placebo and SOC are considered as a single treatment in these NMA which may omit the potential placebo effect.[21]

Therefore, we aimed to collect all RCTs comparing any kinds of pharmacological interventions with placebo or SOC among SARS-CoV-2 and SARS-CoV patients and conduct a NMA to assess comparative efficacy and safety for these treatments.

Materials and Methods

This study was registered on the International Prospective Register of Systematic Review PROSPERO, number CRD42020168178. The study was conducted according to the PRISMA-NMA checklist.

Data sources and searches

PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, and three Chinese databases including SinoMed, China National Knowledge Infrastructure, and WanFang Database were searched from inception to July 20, 2020 [Supplementary Appendix 1, http://links.lww.com/CM9/A707 for full details about search strategy]. In addition, we also checked the reference list of all relevant articles to identify additional studies.

Study selection

Only RCTs written in English or Chinese with available outcome data in which different pharmacological interventions compared in patients with suspected or confirmed SARS-CoV-2 or SARS-CoV were included. Pharmacological interventions were defined according to recommended guidelines,[2-5] including antiviral agents (ribavirin [RIB], lopinavir/ritonavir [LPV_RIT], remdesivir [REM], baloxavir marboxil, favipiravir [FAV], umifenovir [UMI], azvudine, and darunavir/cobicistat), antibiotics (azithromycin [AZI], lincocin, fluoroquinolone, cefoperazone-sulbactam, levofloxacin, and quinolone), COR, CQ, TCM, CON_PLA, α-lipoic acid (ALA), ruxolitinib (RUX), novaferon (NOV), colchicine (COL), IFN, octagam (IVIG), SOC, and placebo (PLA). The primary outcomes of interest included mortality, cure rate, viral negative conversion (VNC), and overall adverse events (OAEs) rate. Secondary outcomes included diarrhea (DIA), acute kidney injury (AKI), transaminase elevation (TE), secondary infection (SEI), heart failure (HF), acute respiratory dyspnea syndrome (ARDS), serious adverse event (SAE), hospitalization duration (HD), and time to fever resolution (TFR). The eligibility of studies for inclusion criteria was assessed independently by six reviewers (XMC, XYT, SC, XYZ, JXZ, and QXZ) in duplicate. Any discrepancies were resolved by consensus between other independent reviewers (FS, JXZ, and QXZ).

Data extraction and quality assessment

Data were extracted with respect to trial information (author, publication year, country, virus type, preprint or not, guideline or not, sample size, trial duration, types of intervention, and control), population characteristics (mean age ± standard deviation [SD], the proportion of female, disease severity), reported outcomes (number of events for dichotomous outcomes and mean with SD for continuous outcomes), and information on methodology. Four investigators (FS, XYZ, JXZ, and QXZ) extracted data independently in duplicate. The risk of bias was assessed according to the Cochrane risk of bias tool.[22] Additionally, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to assess the quality of evidence contributing to each network estimation, which characterizes the quality of a body of evidence on the basis of study limitations, imprecision, inconsistency, indirectness, and publication bias.[23]

Data synthesis and analysis

Methods for direct treatment comparisons

Pairwise meta-analysis was performed using DerSimonian-Laird random-effects model. Odds ratio (OR) and weighted mean difference (WMD) with 95% confidence interval (CI) were calculated as effect measures for dichotomous and continuous outcomes, respectively. The I^2-statistic was calculated as a measure of the proportion of overall variation that is attributable to between-study heterogeneity. For studies with zero-event in both arms, a continuity correction of 0.5 was used.[24] Besides, subgroup pairwise meta-analysis was conducted according to different virus types (SARS-CoV-2 and SARS-CoV).

Methods for indirect and mixed comparisons

A random-effects NMA within the Bayesian framework[25] was then performed by 100,000 iterations with 20,000

adaptations and thinner equal to 10. OR and WMD with 95% CI were summarized for dichotomous and continuous outcomes, respectively. We estimated ranking probabilities for all treatments of being at each possible rank for each intervention. The treatment hierarchy was summarized and reported as the surface under the cumulative ranking curve (SUCRA), mean ranks, and rank-heat plot.[26]

Examination of assumptions in NMA (consistency, transitivity, and heterogeneity)

To check the assumption of consistency in the entire analytical network, a design-by-treatment approach was used.[27] The node splitting method was used to assess the inconsistency of the model by separating evidence on a particular comparison into direct and indirect evidence. Heterogeneity was assessed with common tau^2 statistics and predictive intervals.[28] The transitivity assumption was evaluated by comparing the distribution of clinical variables, which could act as effect modifiers across treatment comparisons. A contribution table was used to assess the contribution of each direct comparison to the estimation of each network meta-analytic summary effect.[28] Additionally, a comparison-adjusted funnel plot was used to detect potential publication bias for outcomes with at least ten trials.

All analyses were conducted using R 4.0.2 (gemtc package for NMA and node-split analysis; ggplot2 package for network evidence plot, forest plots, and cumulative rank probability graphs; netmeta package for funnel plot; fields package, RColorBrewer package, and circlize package for rank-heat plot), STATA (StataCorp LP, Texas, USA) 13.0 (pairwise meta-analysis, estimation of local heterogeneity, and contribution plot), and CINEMA website (https://cinema.ispm.unibe.ch/ for GRADE results).

Results

Study characteristics

Of 45,778 studies retrieved from the searchers, 66 trials with 32 treatments (19,095 patients) met inclusion criteria [Figure 1], including eight different antiviral agents, six antibiotics, high and low dose CQ (CQ_HD, CQ_LD), five add-on treatments (LPV_RIT_IFN, LPV_RIT_RIB_IFN, RIB_IFN, NOV_LPV_RIT, CQ_LD_AZI), COR, TCM, CON_PLA, ALA, RUX, NOV, COL, IFN, IVIG, SOC, and PLA. Among these treatments, six antibiotics were separately compared in one trial for SARS-CoV[29] and one trial for SARS-CoV-2,[30] which could not be connected with other treatments in the trial network. Excluding the six antibiotics, 26 treatments within 64 trials were finally analyzed in the network.

A total of 90.6% (58/64) of trials were two-arm studies and only 6 were multiple-arm studies [Supplementary Appendix 2, http://links.lww.com/CM9/A707]. Overall, 18,881 patients were involved in the meta-analysis, of whom, 17,416, 14,708, 1197, and 11,698 patients contributed to four outcomes of mortality, cure rate, VNC, and OAE, respectively [Figure 2]. Supplementary Appendix 2, http://links.lww.com/CM9/A707 summarizes the characteristics of included trials. Publication years were focused from 2003 to 2005 for SARS-CoV (20 trials) and 2020 for SARS-CoV-2 (46 trials). Trial duration ranged from 5 to 75 days with a median duration of 15 days (interquartile range [IQR]: 13–28 days). The mean age of included patients was 48.9 years (SD = 9.8 years) and the mean proportion of females was 45.7% (IQR: 40.0–53.5%). Disease severity was mild/moderate in 23 trials and moderate/severe in the others. SOC, TCM, antiviral agents, and CQ were the most common studied drugs, within 51, 31, 20, and 14 trials, respectively, followed by PLA (six trials) and COR (four trials).

Methodological quality and risk of bias results

Among the 66 included trials, allocation concealment and blinding of participants and personnel were not clearly reported in 84.8% and 48.5% of the cases, respectively. By contrast, methods for randomization and incomplete outcome data were appropriately described in a large majority of studies (56.1% and 86.4%, respectively). A total of 31.8% of trials were open-label and 72.7% did not have selective reporting (the remaining 19.7% was unclear due to no related protocol). Additionally, 12.1% of trials were funded by a company and 43.9% did not report funding sources [Supplementary Appendix 3, http://links.lww.com/CM9/A707]. Overall, the risk of bias across the evidence network was relatively low.

Results of a pairwise meta-analysis

The effects of different drugs on mortality, cure rate, VNC, and OAE from pairwise meta-analyses are shown in Supplementary Appendix 4, http://links.lww.com/CM9/A707. TCM and COR were associated with a significant reduction in mortality (OR = 0.33, 95% CI: 0.20–0.55 and OR = 0.85, 95% CI: 0.75–0.96, respectively) and a significant increase in cure rate (OR = 2.17, 95% CI: 1.61–2.92 and OR = 1.17, 95% CI: 1.05–1.30, respectively) compared with SOC. Compared with CQ_LD, CQ_HD showed an evident increase in mortality (OR = 3.33, 95% CI: 1.19–9.35). Compared with SOC, TCM showed a significant decrease in the risk of OAE (OR = 0.52, 95% CI: 0.38–0.71), whereas CQ_HD, IFN, COL, and CQ_LD_AZI were all associated with increased risk, with the ORs ranging from 1.65 (95% CI: 1.11–2.47, CQ_LD_AZI) to 3.83 (95% CI: 1.68–8.70, CQ_HD). CQ_LD was significantly associated with increased risk of OAE *vs*. placebo (OR = 2.75, 1.80–4.20).

Results of NMA

Results of NMA were reported in Figures 3 and 4. A significant decrease in mortality was observed for TCM (OR = 0.34, 95% CI: 0.20–0.56) and COR (OR = 0.84, 95% CI: 0.75–0.96) *vs*. SOC, while CQ_HD could significantly increase the risk (OR = 3.20, 95% CI: 1.18–8.73). Besides, a significant reduction in mortality was detected for TCM *vs*. COR, CQ_HD, and CQ_LD with the ORs.

Regarding cure rate, the pooled results favor TCM (OR = 2.16, 1.60–2.91) and COR (OR = 1.17, 1.05–

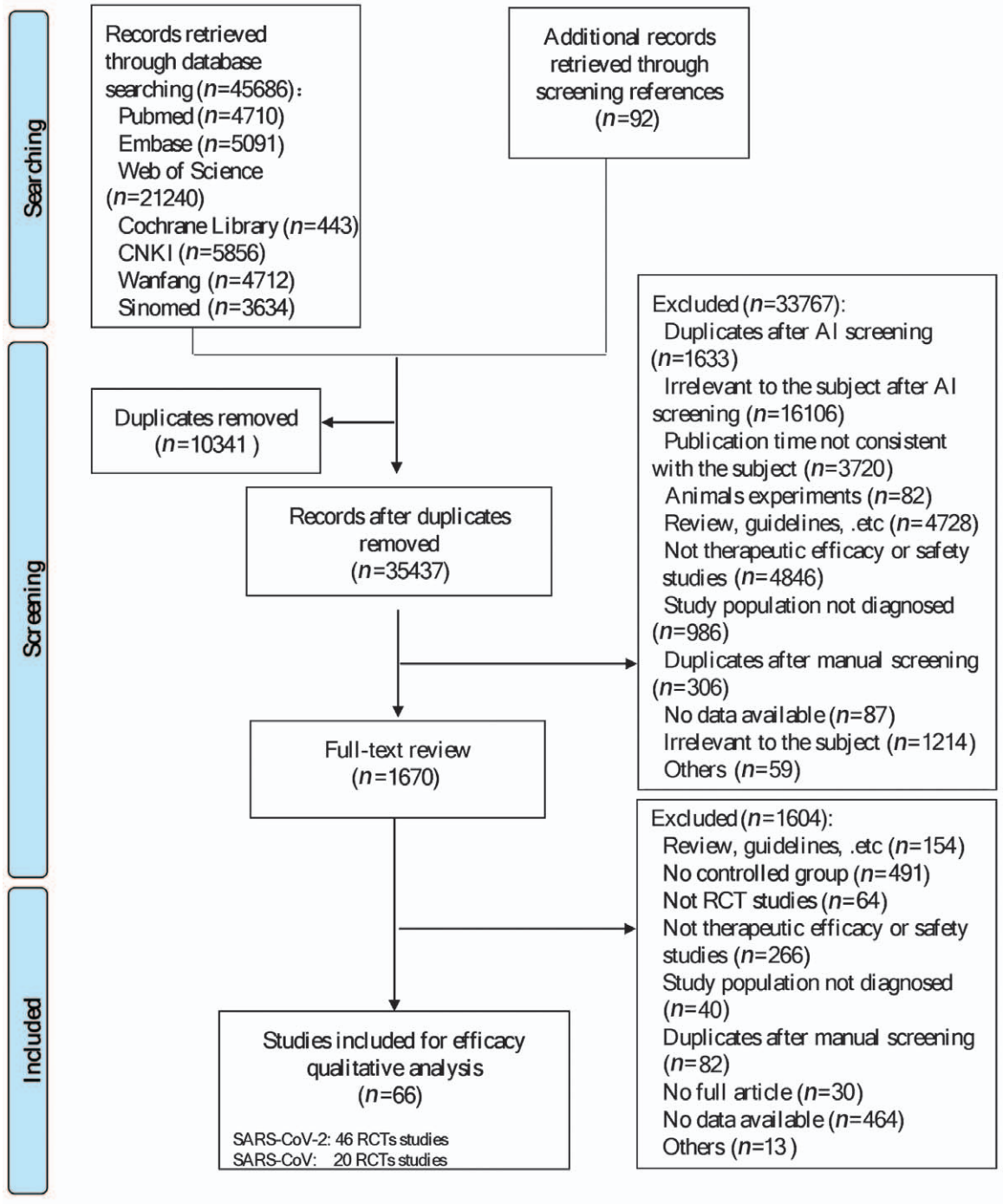

Figure 1: Flowchart of studies considered for inclusion. ALA: α-Lipoic acid; ARDS: Acute respiratory dyspnea syndrome; AZV: Azvudine; BAL: Baloxavir marboxil; CON_PLA: Convalescent plasma; CQ_HD: High doses of chloroquine; CQ_LD: Low doses of chloroquine; COR: Corticosteroids; CQ_LD_AZI: Low doses of chloroquine + azithromycin; COL: Colchicine; DIA: Diarrhea; DRV_c: Single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat; FAV: Favipiravir; HD: Hospitalization duration; HF: Heart failure; IFN: Interferon-β-1a; IVIG: Octagam 10%; LPV_RIT: Lopinavir/ritonavir; LPV_RIT_IFN: Lopinavir/ritonavir + interferon-β-1b; LPV_RIT_RIB_IFN: Lopinavir/ritonavir + ribavirin + interferon-β-1b; LEV_AZI_IFN_COR: Levofloxacin + azithromycin + IFN-α + methylprednisolone; NOV: Novaferon; NOV_LPV_RIT: Novaferon + lopinavir/ritonavir; OAE: Overall adverse event; PLA: Placebo; QUI_AZI_IFN_COR: Quinolone + azithromycin + IFN-α + methylprednisolone; REM_10: Remdesivir 10 mg/day; REM_5: Remdesivir 5 mg/day; RIB_CEFs: Ribavirin + cefoperazone-sulbactam; RIB_IFN: Ribavirin + interferon-β-1b; RUX: Ruxolitinib; SAE: Serious adverse event; SEI: Secondary infection; SOC: Standard of care; TCM: Traditional Chinese medicine; TE: Transaminase elevation; TFR: Time to fever resolution; UMI: Umifenovir; VNC: Viral negative conversion.

1.30) in comparison with SOC. When compared with COR and CQ_LD, TCM could significantly improve the cure rate with an OR of 1.85 (95%CI=1.35–2.56) and 2.38 (95%CI=1.72–3.33), respectively. No significant results were observed on VNC for any comparison.

In terms of OAE, both TCM (OR = 0.52, 95% CI: 0.38–0.70) and REM_10 (OR = 0.31, 95% CI: 0.19–0.52) were associated with decreased risk, whereas COL, CQ_HD, and IFN were associated with increased risk *vs*. SOC, with the ORs ranging from 2.51 (95% CI: 1.20–5.24, CQ_HD)

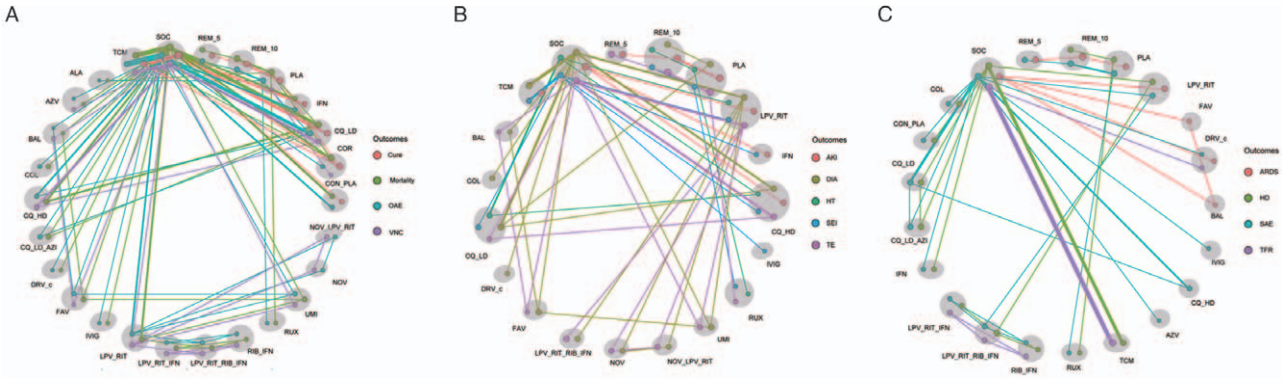

Figure 2: Evidence structure of eligible comparisons for network meta-analysis. (A) Primary outcomes including mortality, cure, VNC, and OAE. (B) Secondary outcomes including DIA, AKI, TE, SEI, and HF. (C) Secondary outcomes including ARDS, SAE, HD, and TFR. Lines connect the interventions that have been studied in head-to-head (direct) comparisons in the eligible RCTs. The width of the lines represents the cumulative number of RCTs for each pairwise comparison and the size of every node is proportional to the number of randomized participants (sample size). AKI: Acute kidney injury; ALA: α-Lipoic acid; ARDS: Acute respiratory dyspnea syndrome; AZV: Azvudine; BAL: Baloxavir marboxil; CON_PLA: Convalescent plasma; CQ_HD: High doses of chloroquine; CQ_LD: Low doses of chloroquine; COR: Corticosteroids; CQ_LD_AZI: Low doses of chloroquine + azithromycin; COL: Colchicine; DIA: Diarrhea; DRV_c: Single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat; FAV: Favipiravir; HD: Hospitalization duration; HF: Heart failure; IFN: Interferon-β-1a; IVIG: Octagam 10%; LPV_RIT: Lopinavir/ritonavir; LPV_RIT_IFN: Lopinavir/ritonavir + interferon-β-1b; LPV_RIT_RIB_IFN: Lopinavir/ritonavir + ribavirin + interferon-β-1b; LEV_AZI_IFN_COR: Levofloxacin + azithromycin + IFN-α + methylprednisolone; NOV: Novaferon; NOV_LPV_RIT: Novaferon + lopinavir/ritonavir; OAE: Overall adverse event; PLA: Placebo; QUI_AZI_IFN_COR: Quinolone + azithromycin + IFN-α + methylprednisolone; RIB_CEFs: Ribavirin + cefoperazone-sulbactam; REM_10: Remdesivir 10 mg/day; REM_5: Remdesivir 5 mg/day; RIB_IFN: Ribavirin + interferon-β-1b; RUX: Ruxolitinib; SAE: Serious adverse event; SEI: Secondary infection; SOC: Standard of care; TCM: Traditional Chinese medicine; TE: Transaminase elevation; TFR: Time to fever resolution; UMI: Umifenovir; VNC: Viral negative conversion.

to 3.81 (95% CI: 1.55–9.29, COL). In comparison with COL, COR, CQ_HD, CQ_LD, IFN, and LPV_RIT, a significant reduction of OAE was found for TCM.

Results of NMA for secondary outcomes are listed in Supplementary Appendix 5, http://links.lww.com/CM9/A707. Among separate adverse events (AEs), a significantly increased risk of DIA was detected for COL, CQ_HD, CQ_LD, LPV_RIT, and LPV_RIT_RIB_IFN *vs*. SOC (OR ranging from 3.80 [95% CI: 1.55–9.26, COL] to 9.62 [95% CI: 1.70–56.11, LPV_RIT]) and TCM (OR ranging from 8.77 [95% CI: 2.99–25.74, COL] to 22.27 [95% CI: 3.53–142.16, LPV_RIT]). Meanwhile, TCM showed a significant decrease in the risk of DIA (OR = 0.43, 95% CI: 0.24–0.79) and SEI (OR = 0.33, 95% CI: 0.17–0.64) when compared with SOC. Additionally, an evident reduction of ARDS was found for LPV_RIT *vs*. SOC (OR = 0.37, 95% CI: 0.18–0.80). No other significant results were detected for other separate AEs (AKI, SAE, TE, and HF).

TCM, RIB_IFN, CON_PLA, LPV_RIT_RIB_IFN, and LPV_RIT were all associated with shorter hospitalization lengths ranging from −17.80 (95% CI: −29.92 to −5.74, RIB_IFN) to −2.53 (95% CI: −3.43 to −1.63, TCM) days when compared with SOC. Furthermore, TCM could reduce hospitalization length for 2.63 (CQ_LD) to 5.09 (IFN) days *vs*. CQ_LD, CQ_LD_AZI, and IFN. Besides, a significant reduction in TFR was found for TCM *vs*. SOC (WMD = −1.03 days, 95% CI: −1.09, −0.97).

According to contribution tables of the network [Supplementary Appendix 6, http://links.lww.com/CM9/A707], comparison of SOC *vs*. antiviral agents, COR and CQ had the largest contribution in all four entire networks for primary outcomes with 51.8%, 56.5%, 56.9%, and 50.0% for mortality, cure rate, VNC, and OAE, respectively.

Transitivity, inconsistency, and heterogeneity

Assessment of transitivity by box plots indicated mean age and proportion of females across treatment comparisons were relatively similar [Supplementary Appendix 7, http://links.lww.com/CM9/A707]. The test for global inconsistency did not detect any significant difference between consistency and inconsistency models for all the four primary outcomes ($P = 0.994$ for mortality, $P = 0.763$ for the cure, $P = 0.952$ for VNC, and $P = 0.773$ for OAE, respectively) and three secondary outcomes ($P = 0.984$ for DIA, $P = 0.845$ for SAE, and $P = 0.614$ for TE, respectively), except for other six secondary outcomes (AKI, ARDS, HD, HF, SEI, and TFR) could not conduct consistency test due to no loop in the whole network. The test for inconsistency from the node-splitting model showed no significant difference in all comparisons across all outcomes [Supplementary Appendix 8, http://links.lww.com/CM9/A707]. Most comparisons in all 13 outcomes were with low heterogeneity as indicated in the predictive interval. At visual inspection, funnel plots for all seven outcomes with a number of studies >10 [Supplementary Appendix 9, http://links.lww.com/CM9/A707] were symmetric and did not suggest any significant risk of publication bias.

Rank-heat plot and SUCRA of all treatments

Figure 5 and Supplementary Appendix 10, http://links.lww.com/CM9/A707 show the mean values of SUCRA for providing the hierarchy ranking of different treatments on all 13 outcomes. Due to sparse network data and non-definitive results in most comparisons, the ranking might be biased and interpretation should be made with caution.

GRADE evaluation on the quality of evidence

According to GRADE, the quality of evidence ranged between very low and moderate [Supplementary Appendix

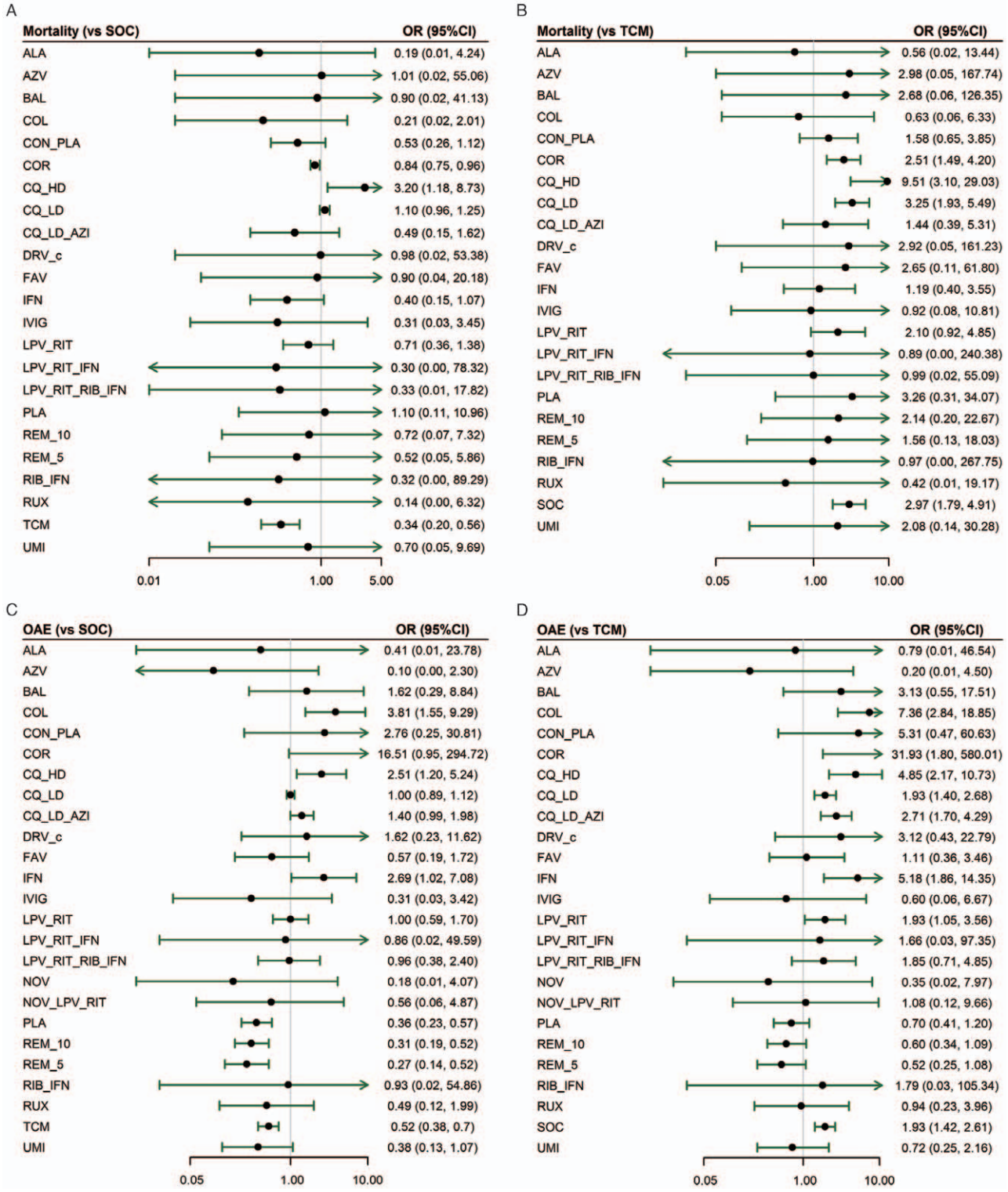

Figure 3: Results of network meta-analysis for mortality and OAE. (A) Mortality compared with SOC. (B) Mortality compared with TCM. (C) OAE compared with SOC. (D) OAE compared with TCM. ALA: α-Lipoic acid; AZV: Azvudine; BAL: Baloxavir marboxil; CON_PLA: Convalescent plasma; CQ_HD: High doses of chloroquine; CQ_LD: Low doses of chloroquine; COR: Corticosteroids; CQ_LD_AZI: Low doses of chloroquine + azithromycin; COL: Colchicine; DRV_c: Single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat; FAV: Favipiravir; IFN: Interferon-β-1a; IVIG: Octagam 10%; LPV_RIT: Lopinavir/ritonavir; LPV_RIT_IFN: Lopinavir/ritonavir + interferon-β-1b; LPV_RIT_RIB_IFN: Lopinavir/ritonavir + ribavirin + interferon-β-1b; NOV: Novaferon; NOV_LPV_RIT: Novaferon + lopinavir/ritonavir; OAE: Overall adverse event; OR: Odds ratio; PLA: Placebo; REM_10: Remdesivir 10 mg/day; REM_5: Remdesivir 5 mg/day; RIB_IFN: Ribavirin + interferon-β-1b; RUX: Ruxolitinib; SOC: Standard of care; TCM: Traditional Chinese medicine; UMI: Umifenovir.

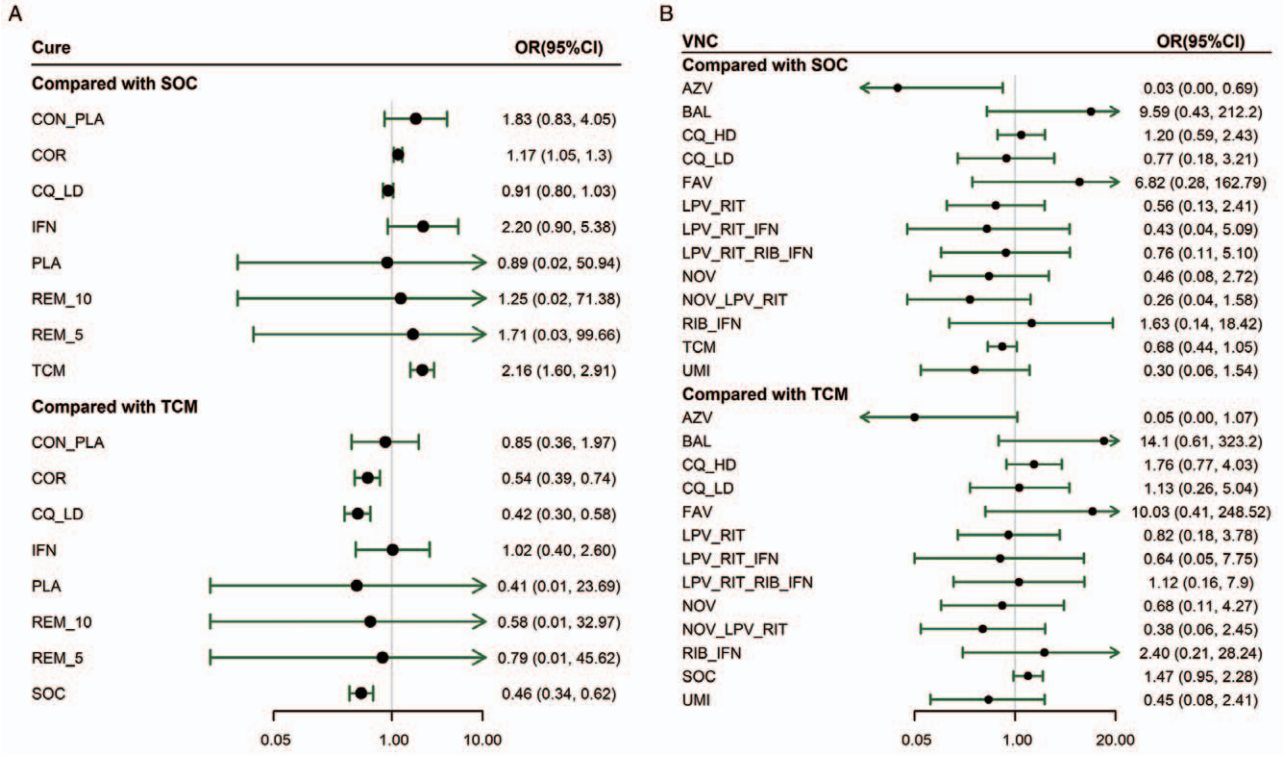

Figure 4: Results of network meta-analysis for cure and VNC compared with SOC and TCM. (A) Cure. (B) VNC. ALA: α-Lipoic acid; AZV: Azvudine; BAL: Baloxavir marboxil; CON_PLA: Convalescent plasma; CQ_HD: High doses of chloroquine; CQ_LD: Low doses of chloroquine; COL: Colchicine; CQ_LD_AZI: Low doses of chloroquine + azithromycin; COR: Corticosteroids; DRV_c: Single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat; FAV: Favipiravir; IFN: Interferon-β-1a; IVIG: Octagam 10%; LPV_RIT: Lopinavir/ritonavir; LPV_RIT_IFN: Lopinavir/ritonavir + interferon-β-1b; LPV_RIT_RIB_IFN: Lopinavir/ritonavir + ribavirin + interferon-β-1b; NOV: Novaferon; NOV_LPV_RIT: Novaferon + lopinavir/ritonavir; OR: Odds ratio; PLA: Placebo; REM_10: Remdesivir 10 mg/day; REM_5: Remdesivir 5 mg/day; RIB_IFN: Ribavirin + interferon-β-1b; RUX: Ruxolitinib; SOC: Standard of care; TCM: Traditional Chinese medicine; UMI: Umifenovir; VNC: Viral negative conversion.

11, http://links.lww.com/CM9/A707]. In terms of TCM *vs*. SOC, the quality was moderate for mortality, low for cure rate, and very low for VNC and OAE. As for COR *vs*. SOC, the quality was low for mortality, cure rate, and OAE while very low for VNC. Regarding CQ_HD *vs*. SOC, the quality was low for mortality and very low for OAE.

Subgroup analyses

In addition, subgroup pairwise meta-analysis by virus type confirmed the beneficial effect on mortality and cure rate of TCM and COR *vs*. SOC, reduction effect on OAE of TCM *vs*. SOC, increased risk of mortality for CQ_HD *vs*. CQ_LD, and increased risk of OAE for CQ_HD, IFN, and CQ_LD_AZI *vs*. SOC in SARS-CoV-2, which were in agreement with those previous produced [Supplementary Appendix 12, http://links.lww.com/CM9/A707].

Discussion

Considering the global pandemic of COVID-19, increasing attention is being paid to the effectiveness and safety of pharmacological treatments. Our NMA with 66 trials and 19,095 patients suggested that COR and TCM could probably reduce mortality and increase cure rate with no increased risk of OAEs compared with SOC. However, CQ_HD might increase the risk of mortality. CQ, IFN, and other antiviral agents could increase the incidence of OAEs.

In line with other studies,[7,9,18,31-35] we did not find any potential effect on reducing mortality or increasing cure/viral clearance rate for IFN and any antiviral agents, but rather we found CQ_HD was associated with increased mortality. It should be recognized that several side-effects may be caused according to some observational studies and trials, such as QT prolongation by CQ and FAV, gastrointestinal complications by LPV_RIT and UMI.[18,31-35] In our study, an increased risk of OAE was detected for CQ and IFN, and DIA for LPV_RIT and LPV_RIT_RIB_IFN, although no other significant risk of OAE was detected for antiviral agents. Given the potential harms with lack of effectiveness, they are not recommended by several guidelines as a treatment for COVID-19, particularly for mild to moderate patients.[2-5] For severe patients who need supplemental oxygen or intensive care, REM is weakly recommended to shorten the time to clinical improvement.[5] However, the evidence was low- or very low-quality with no observed effect on HD and mortality.

According to the World Health Organization and other guidelines, routine use of systematic COR was not recommended for the treatment of viral pneumonia, except for patients who require supplemental oxygen

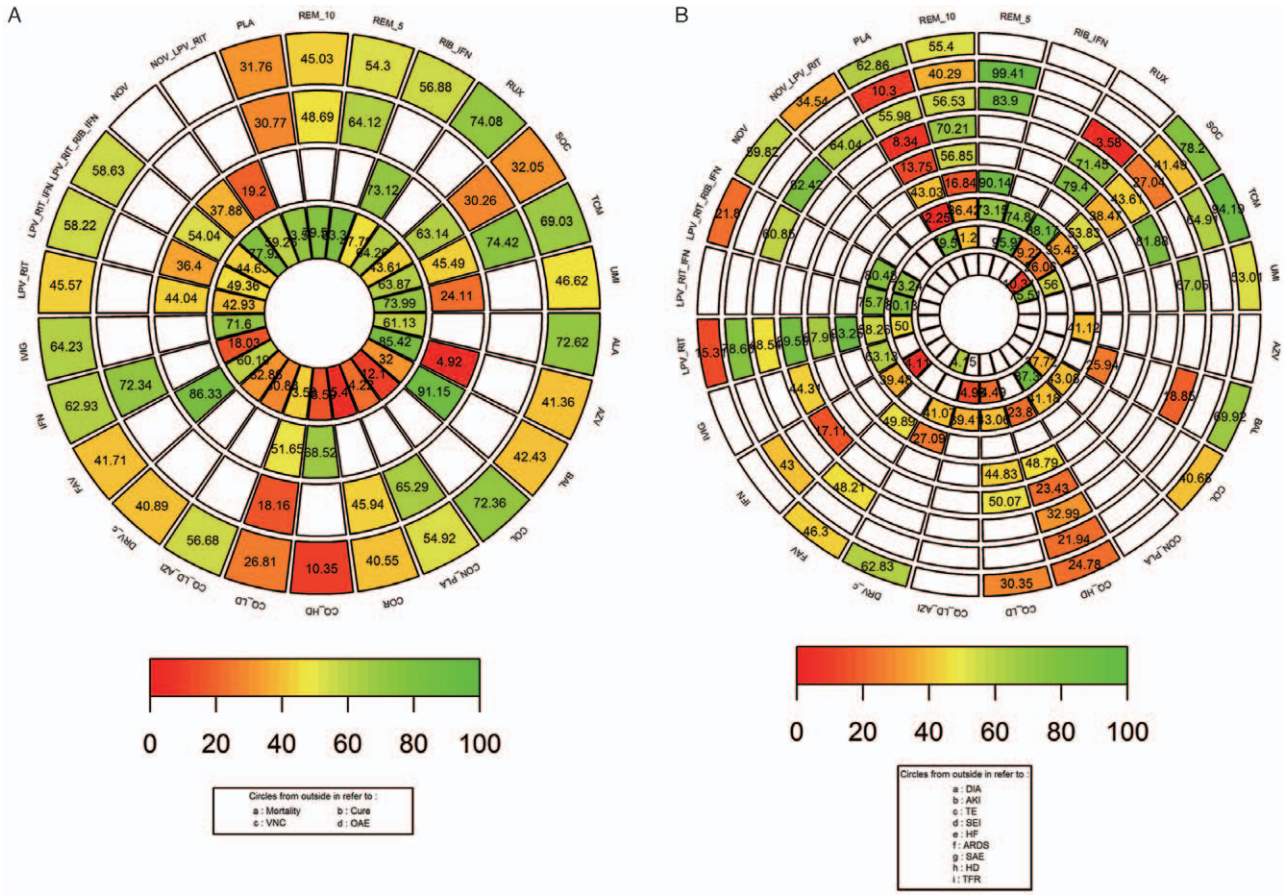

Figure 5: Rank-heat plots for each outcome. (A) Primary outcomes (mortality, cure, VNC, OAE). (B) Secondary outcomes (DIA, AKI, TE, SEI, HF, ARDS, SAE, HD, and TFR). The rank-heat plot of 19 and 17 treatments (presented in radii) for four primary outcomes and nine secondary outcomes (presented in concentric circles). Each sector is colored according to the SUCRA value of corresponding treatment and outcome using the transformation of three colors: red (0%), yellow (50%), and green (100%). AKI: Acute kidney injury; ALA: α-Lipoic acid; ARDS: Acute respiratory dyspnea syndrome; AZV: Azvudine; BAL: Baloxavir marboxil; CON_PLA: Convalescent plasma; CQ_HD: High doses of chloroquine; CQ_LD: Low doses of chloroquine; COR: Corticosteroids; CQ_LD_AZI: Low doses of chloroquine + azithromycin; COL: Colchicine; DIA: Diarrhea; DRV_c: Single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat; FAV: Favipiravir; HD: Hospitalization duration; HF: Heart failure; IFN: Interferon-β-1a; IVIG: Octagam 10%; LPV_RIT: Lopinavir/ritonavir; LPV_RIT_IFN: Lopinavir/ritonavir + interferon-β-1b; LPV_RIT_RIB_IFN: Lopinavir/ritonavir + ribavirin + interferon-β-1b; LEV_AZI_IFN_COR: Levofloxacin + azithromycin + IFN-α + methylprednisolone; NOV: Novaferon; NOV_LPV_RIT: Novaferon + lopinavir/ritonavir; OAE: Overall adverse event; PLA: Placebo; QUI_AZI_IFN_COR: Quinolone + azithromycin + IFN-α + methylprednisolone; REM_10: Remdesivir 10 mg/day; REM_5: Remdesivir 5 mg/day; RIB_IFN: Ribavirin + interferon-β-1b; RUX: Ruxolitinib; RIB_CEFs: Ribavirin + cefoperazone-sulbactam; SAE: Serious adverse event; SEI: Secondary infection; SOC: Standard of care; SUCRA: Surface under the cumulative ranking curve; TCM: Traditional Chinese medicine; TE: Transaminase elevation; TFR: Time to fever resolution; UMI: Umifenovir; VNC: Viral negative conversion.

and mechanical ventilation.[2-4] A systemic inflammatory response may develop in patients with severe COVID-19, which could result in lung injury and multisystem organ dysfunction. Since COR could decrease the inflammatory response, it might lead to fewer intensive care unit transfers, thereby lowering the mortality rate. Several studies, including RECOVERY trial[36] and meta-analyses,[13,18] show similar findings. However, in mild or moderate patients, this benefit may be outweighed by adverse effects such as delayed viral clearance and increased risk of SEI. Results from different studies are not consistent. A meta-analysis[37] of 6458 patients with influenza pneumonia indicated a 75% and 98% increase in mortality and SEI risk, respectively, while a retrospective study[38] of 201 patients with COVID-19 found a 62% decreased risk of mortality for methylprednisolone. Our NMA found improved effects of COR on mortality and cure rate and no effects on VNC and SEI *vs*. SOC, perhaps due to severe pneumonia of included patients with older age (mean age = 66.2 years). Further subgroup and meta-regression NMA according to disease severity are essential upon the completion of many other ongoing trials, since the inclusion of mild, moderate, and severe patients may dilute the effect of COR.

Our study found TCM as adjuvant therapy achieved significantly lower mortality and OAE with a higher cure rate, which is consistent with the previous meta-analysis.[14-16] While the use of traditional herbs remains controversial in clinical practice, the beneficial effect is biologically reasonable.[39-43] The most commonly used herbs were Radix Glycyrrhizae (Gancao), Astragali Radix (Huangqi), Rhizoma Pinelliae Tematae (Banxia), and Forsythiae Fructus (Lianqiao), which could clear away heat and toxic material, eliminate phlegm-dampness, and replenish qi according to TCM theory.[39] Moreover, it has also been confirmed that these herbs have a wide of pharmacological effects including anti-inflammatory, antiviral, antipyretic, antioxidative, and immunoregulatory effects.[40-43] Thus, it could maintain the homeostasis of the

immune system, inhibit various viruses and thereby effectively block the ranging from mild to critical. However, the dosage, composition, treatment duration, and disease severity of COVID-19 cases should be taken into account when considering TCM, since these factors are closely related to safety issues. Despite a lower AE rate in TCM compared with SOC, most trials included in our study were unblinded with low quality. Therefore, further well-designed studies are needed to investigate the safety issues of TCM.

Compared with previous relevant meta-analyses, a major strength of our study is the comprehensive search and analysis of effectiveness and safety profiles for all kinds of pharmacological treatments in a whole network with the largest number of studies and sample size. Furthermore, we included all pharmacological treatments recommended by several guidelines,[2-5] including TCM and CON_PLA as well as other treatments evaluated in the previous meta-analysis. Meanwhile, placebo and SOC were separated as two treatment nodes in our evidence network, which could minimize bias due to the potential placebo effect.[21] Additionally, we assessed the quality of evidence and incorporate it into explaining the results by the GRADE framework.

Several limitations, however, should be mentioned. First, most comparisons were assessed as low or very low quality in the GRADE framework with wide CIs owing to sparse data, which might restrict the interpretation of results. However, these data are still valuable and timely at this stage with no effective specific drugs for COVID-19. When more data of ongoing trials are available, we will update the analysis. Second, the methodology of some included trials was poor. Nearly 80% of trials were not performed well in blinding or concealment allocation. Thus, this may introduce bias and results should be interpreted with caution. However, it might be difficult to conduct double-blind trials for a contagious disease in some clinical situations. Finally, due to sparse data and unavailable access to original trial data, we could not perform detailed NMA subgroup analyses, meta-regression, or individual patient data meta-analysis to properly address potentially relevant effect modifiers, such as age, disease severity, concomitant therapy, and treatment duration.

Conclusions

COR and TCM may reduce mortality and increase cure rate with no increased risk of OAEs compared with standard care. However, CQ_HD might increase the risk of mortality. CQ, IFN, and other antiviral agents could increase the incidence of OAEs. A majority of trials are small-scale trials with important methodological limitations, and no definitive conclusion could be drawn for most treatments. The current evidence is generally uncertain with low-quality and further high-quality trials are needed.

Acknowledgements

The authors gratefully appreciate the excellent work for Xian-Ming Cai, Shan Cai, and Xiao-Yu Tan (Peking University). Special thanks to their meticulous help with study selection.

Funding

This study is funded by grants from the National Natural Science Foundation of China (No. 72074011), the Special Project for Major Infectious Disease of Peking University Health Program of China (No. BMU2020HKYZX010), and the National Key Technology R&D Program of China (No. 2020YFC0840800).

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no potential conflicts of interest relevant to this article.

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How to cite this article: Wu SS, Zhou QX, Zeng XY, Zhang JX, Yang ZR, Yang QQ, Zhang ZL, Chen YH, Sun F, Zhan SY. Comparative effectiveness and safety of 32 pharmacological interventions recommended by guidelines for coronavirus disease 2019: a systematic review and network meta-analysis combining 66 trials. Chin Med J 2021;134:1920–1929. doi: 10.1097/CM9.0000000000001672