Systematic Review and Meta-Analysis

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The therapeutic effect and safety of the drugs for COVID-19

A systematic review and meta-analysis

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has spread almost all regions of the world and caused great loss to the whole body of mankind. Thus, numerous clinical trials were conducted to find specific medicine for COVID-19 recently. However, it remains unanswered whether they are beneficial.

Objective: This study aimed to evaluate the efficiency and safety of the COVID-19 medicine.

Methods: Studies were determined through searching PubMed, Embase, Cochrane Library, and Medline. The studies of COVID-19 medicine were involved with eligible end points containing mortality, discharge rate, rate of clinical improvement, and rate of serious adverse events.

Results: A total of 33 studies involving 37,879 patients were included in our study, whose intervening measures contained three major types of COVID-19 medicine, ACEI/ARB, antiviral medicine, and chloroquine/hydroxychloroquine. Compared to control group, COVID-19 drugs have no distinct effect on mortality (RR, 0.93; 95% CI, 0.79–1.11, $P = .43$) and discharge rate (RR, 1.06; 95% CI, 0.98–1.14, $P = .13$). However, antiviral medicine presents the obvious advantage in clinical improvement (RR, 1.11; 95% CI, 1.01–1.23, $P < .05$). In addition, the serious adverse events rate (RR, 0.75; 95% CI, 0.63–0.88, $P < .05$) of COVID-19 medicine is lower than control group.

Conclusion: The results indicated antiviral medicine was potential specific medicine for COVID-19 treatment by improving clinical symptoms, but it failed to increase the discharge rate and reduce mortality. Chloroquine/hydroxychloroquine and ACEI/ARB had no significant effect on treatment of COVID-19, thus they were not recommended for routine medication. Moreover, more trials are needed to find effective drugs to lower the mortality of COVID-19 patients.

Abbreviations: ACE2 = angiotensin-converting enzyme 2, ACEI = Angiotensin-converting enzyme inhibitors, ARB = angiotensin-receptor blockers, CI = confidence intervals, COVID-19 = coronavirus disease 2019, HCQ = hydroxychloroquine, IFN = interferon, NOS = Newcastle-Ottawa Scale, RAAS = renin-angiotensin-aldosterone system, RCT = randomized controlled trials, RR = risk ratio, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SOC = standard of care.

Keywords: COVID-19, efficiency, drugs, meta-analysis, safety

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RQ and JL contributed equally to this work.

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1. Introduction

In December 2019, an outbreak of novel pneumonia swept through Wuhan, Hubei province, which was proved to be caused by a novel kind of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) later.[1,2] Due to its high infectivity, the novel pneumonia quickly spread around the world and was named coronavirus disease 2019 (COVID-19) by WHO.[3] Up to now, COVID-19 has hit more than 200 Countries and regions,[4] resulting in great loss of material resources, financial and manpower.

For better battling against the disease, scientific researchers and medical workers around the world have been searching for appropriate methods to control the outbreak, such as isolation of patients, wearing N95, KN95 masks and timely treatment of patients.[5,6] Because SARS-CoV-2 is a novel virus, and its properties are still unknown, treatment is one of the major difficulties among them. Therapeutic options for the COVID-19 are mainly divided into etiological treatment and symptomatic treatment. Symptomatic treatment means treating complications of diseases. For example, fever and hypoxia are common complications of COVID-19 patients,[7,8] thus symptomatic treatment for them are oxygen inhalation and quelling fever. Etiological treatment for COVID-19 is using antiviral medicine or products of SARS-CoV-2 to suppress propagation of the virus.[9] Nevertheless, there remain lacks specific medicine for COVID-19. The COVID-19 medicine can be generally divided into Angiotensin-converting enzyme inhibitors (ACEI)/angiotensin-receptor blockers (ARB), antiviral medicine and chloroquine/hydroxychloroquine. ACEI/ARB is frequently used for hypertension therapy and hypothesized to suppress the combination between SARS-CoV-2 and its receptors, which probably cure the COVID-19. However, its safety is uncertain.[10] The common antiviral medicine for COVID-19 is remdesivir, lopinavir/ritonavir, and so on. In vitro study, they exerted their antiviral effect at low concentration and with the high selectivity index,[11] demonstrating their potential for treatment of COVID-19. Therefore, in order to find appropriate etiological treatment as quickly as possible, hundreds of clinical trials have been started to evaluate the efficiency and safety of these medicine or products. Nevertheless, the current results of trials are controversial. The first report of clinical trial results showed that lopinavir/ritonavir failed to improve the clinical symptoms significantly.[12] In contrast, the clinical data of remdesivir showed that remdesivir prominently shortened the time of clinical improvement and reduced the mortality of severe COVID-19 patients.[13] Furthermore, clinical data of chloroquine indicated it may not be the efficient medicine similarly.[14] Even worse, the mortality of the patients was higher after using chloroquine.[14] However, study of Gao et al showed an apparent efficacy in treatment of COVID-19 patients.[15]

Due to the inconsistencies of clinical results, scientific methods should be adopted to comprehensively evaluate the efficacy and safety of existing medicine and products of COVID-19. Therefore, this study summarized the published clinical data of them and evaluated their safety efficiency. Moreover, we also compared efficiency and safety indicators among different kinds of medicine and products of COVID-19, hoping to provide evidence for clinical treatment.

2. Materials and methods

This study is a meta-analysis and systematic review of clinical trials including randomized controlled trials (RCTs) and non-RCTs which focus on the efficiency or safety of the COVID-19 medicine. In addition, all processes of this study are based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16]

2.1. Research strategy

Keywords associated with the clinical trial of COVID-19 including COVID-19 (coronavirus disease 2019 or COVID-19 or severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2) and trials of treatment (trial or clinical trial or treatment or therapy or medicine or ARB/ACEI or HCQ) were adopted to search in PubMed, Embase, Cochrane Library, and Medline from January 2020 to February 2021. The types of publication and language are not restricted, except for unpublished trials. Moreover, the complete data of studies were enrolled for judgement of repeated trials.

2.2. Inclusion criteria and selection of the studies

Inclusion and exclusion criteria were predetermined. The eligible studies were included according to the following criteria: Patients: confirmed COVID-19 cases (age $\geq$ 18); Intervention: patients in experimental group were received medicine therapy of COVID-19, with the addition of basic treatment as control group; Control group: basic treatments or placebo; Outcomes: efficiency (e.g., mortality, discharge rate, clinical improvement rate), Safety (e.g., rate of adverse events); Study types: clinical trials were adopted. Studies which met the following criteria were excluded: data is lacking or incomplete; duplicated studies; studies published in form of reviews, meta-analysis, case reports, letters, editorials, or commentaries.

The title and abstract were firstly screened by two reviewers independently. Then, for further screening the articles that were difficult to distinguish through title/abstract, the full texts were retrieved for evaluation. All the disagreements were solved via discussion between two reviewers or opinions of the third party.

2.3. Data extraction and quality evaluation

First author, year of publication, number of patients, therapeutic method, and type of study were extracted in every study. Furthermore, the extractable efficiency indicators (mortality, discharge rate, improvement rate) or safety indicator (serious adverse events) were obtained in trails.

The quality of RCTs included was evaluated via Cochrane Handbook,[17] which is composed of six items: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, no selective outcome reporting and other sources of bias. Items identified as "low risk" are considered appropriate. Total score of the study is 6. The higher the score, the better the quality of the study.

The Newcastle-Ottawa Scale (NOS) assesses the quality of Non-RCTs with eight questions: case definition adequate; representativeness of the Cases; selection of controls; definition of controls; comparability of cases and controls; ascertainment of exposure; use the same method to determine case and control exposure factors; non-response rate. The range of score is 0 to 9. In addition, the higher the score, the better the quality of the study.

2.4. Statistical analysis

Review Manager (version 5.3; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) was adopted to conduct statistical analysis. For efficiency and safety outcomes, the risk ratio (RR) was adopted, which were calculated through the 95% confidence intervals (CI), with the employ of random effect model in consideration of the heterogeneity of COVID-19 medicine.[18] Statistical heterogeneity was calculated through I^2 statistic, and value of >50% was considered as high heterogeneity.[19,20] Publication bias was detected by funnel plots if enough articles (>10) were adopted for an outcome. Moreover, sensitivity analyses and subgroup analyses would be performed to explain the sources of heterogeneity if the trials were enough. $P < .05$ is thought to be statistically significant.

3. Result

3.1. Literature research

The screening process was shown in Figure 1, and 4060 studies were identified according to the research strategy initially. In total, 33 studies containing 37,879 patients were adopted in our study and all of them were published in English.[10,12,21–51] Among trails included, 22 of them were RCTs, and the other were Non-RCTs. Furthermore, 9 studies investigated potential efficiency and safety of ACEI/ARB for COVID-19; 15 of them aimed at the antiviral medicine of COVID-19 with remaining 10 studies caring about hydroxychloroquine and chloroquine. Among them, one study focused on hydroxychloroquine and three types of antiviral medicine.

3.2. Characteristics of the studies

All trails (Table 1) were carried out in 2020, which included 11 Non-RCTs and 22 RCTs. Intervention groups of the trails received COVID-19 medicine (antiviral treatment, ACEI/ARB, hydroxychloroquine/chloroquine) plus standard treatment including oxygen inhalation, reducing the fever, and so on. In contrast, the treatment received by control group were standard treatment (symptomatic treatment such as oxygen inhalation, correction of electrolyte imbalance, and so on) with or without simple antiviral medicine. Among the studies, 15,928 patients were allocated to COVID-19 medicine groups while 21,951 patients in control groups. As for the patients received COVID-19 medicine, 1908 patients (12.0%) participated in the trials of ACEI/ARB compared with 10,735 patients (67.4%) and 3285 patients (20.6%) enrolled in the trails of antiviral medicine and hydroxychloroquine/chloroquine. Respectively, 9 studies were conducted for ACEI /ARB for coivd-19, 15 for antiviral medicine of COVID-19, 10 for hydroxychloroquine or chloroquine.

3.3. Quality evaluation of studies

The quality evaluation of the 22 RCTs included was shown (see S1 Table, Supplemental Digital Content, http://links.lww.com/MD2/A62 which presents the quality evaluation of RCTs). All of them showed Sequence generation in detail and no selective outcome reporting, but only 6 studies of them described the method used for allocation concealment together with blinding of participants, personnel and outcome assessors. Additionally, only 3 studies did not describe how to deal with incomplete outcome data. However, only 7 articles showed high risk in other sources of bias. In summary, the qualities of most RCTs selected varied from moderate to high.

Eleven studies included were non-RCTs and assessed for the quality by NOS (See S2 Table, Supplemental Digital Content, http://links.lww.com/MD2/A62 which presents the quality evaluation of non-RCTs). The maximum quality score in NOS is 9, and the range of score of included non-RCTs is 4 to 7, with a median of 6. Among the 11 studies, all of them reported the adequate definition of case, representativeness of the cases, definition of controls and non-response rate. Regrettably, 2 studies omitted the comparability of cases and controls and less than half of studies (5) used the same method to determine case and control exposure factors. Overall, the Non-RCTs included showed a high quality.

3.4. Primary analysis

3.4.1. Efficiency. In general, 31 studies involving treatments of antiviral medicine, ACEI/ARB and hydroxychloroquine/chloroquine were included for mortality evaluation, and there was no obvious in mortality difference between COVID-19 medicine groups and control groups (RR, 0.93; 95% confidence interval [CI], 0.79–1.11, $P = .43$) (Fig. 2). In addition, compared with control groups, COVID-19 medicine had no significant increase in discharge rate (RR, 1.06; 95% confidence interval [CI], 0.98–1.14, $P = .13$) (Fig. 3). The endpoint of clinical improvement rate only existed in the treatment of antiviral medicine, which indicated the clinical improvement rate of antiviral medicine was higher than control group, with a significantly statistical difference (RR, 1.11; 95% confidence interval [CI], 1.01–1.23, $P < .05$) (Fig. 4).

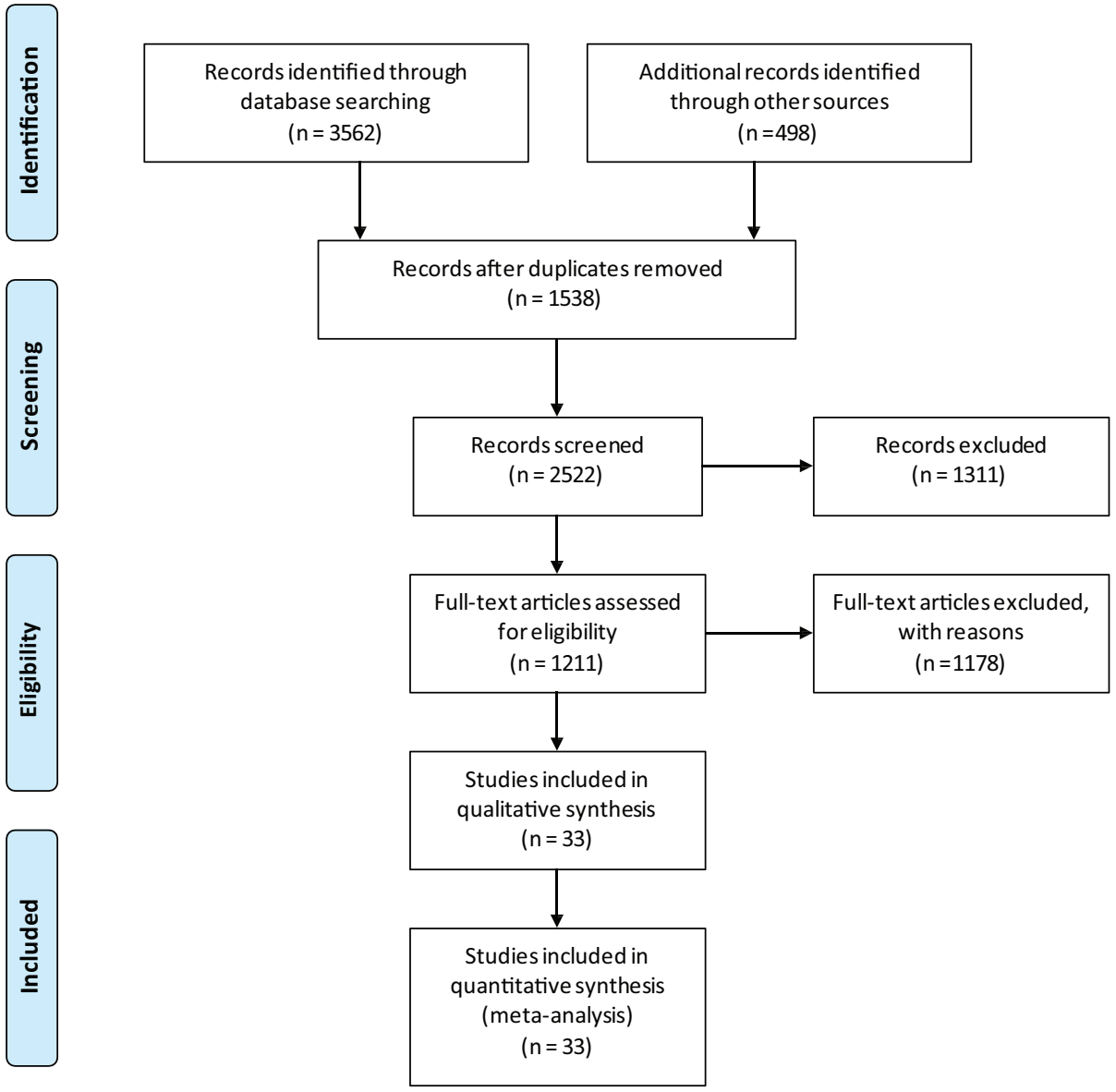
3.4.2. Safety. In terms of safety of new therapies, reduction in occurrence of serious adverse events was achieved in experiment groups which made use of ACEI/ARB, antiviral medicine and hydroxychloroquine/chloroquine in comparison with the standard treatment (RR, 0.75; 95% confidence interval [CI], 0.63–0.88, $P < .05$) (Fig. 5).

3.4.3. Subgroup analysis. In accordance with types of used drugs, studies included were divided into subgroup of ACEI/ARB, subgroup of antiviral medicine, subgroup of hydroxychloroquine/chloroquine respectively, and differences were analyzed and displayed in Figure 6. Like the result that overall drug mortality had no statistical difference, no remarkable reduction existed in mortality of antiviral medicine (RR, 0.91; 95% confidence interval [CI], 0.80–1.04, $P = .16$). Similarly, evidence was insufficient to support any improvement in mortality for subgroups of ACEI/ARB (RR, 0.78; 95% confidence interval [CI], 0.38–1.56, $P = .48$). Furthermore, there was no obvious statistical difference within mortality reduction in subgroups of the hydroxychloroquine/chloroquine compared with control groups (RR, 1.21; 95% confidence interval [CI], 0.88–1.68, $P = .24$).

3.4.4. Bias of publication. Funnel chart was used for the assessment of publication bias, and it revealed there was no obvious bias existed in studies included.

4. Discussion

This analysis included 33 studies with high quality, which involved 37,879 patients and revealed that COVID-19 medicine



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For more information, visit www.prisma-statement.org.

Figure 1. Flow chart of trials retrieval and screening.

had the better therapeutic effect in clinical improvement rate and safety end point than standard of care, but the significant increase in discharge rate and decrease in mortality didn't appear among them. Furthermore, among different types of medicine, none of them could led to obvious reduction in mortality. However, antiviral medicine led to the better clinical improvement than usual therapy, indicating this category of medicine had the potential to be specific medicine of COVID-19.

Table 1

Characteristic of trials included.

First author	Type of study	Location	No. of patients (male)			Treatment	
			Age	Intervention	Control	Intervention	Control
Gao C	Non-RCT	China	58	183 (104)	140 (73)	Antihypertension (RAAS Inhibitor) + SOC	No Antihypertension + SOC
Yang G	Non-RCT	China	66	43 (21)	83 (41)	ARB/ACEI + SOC	Non-ARB/ACEI + SOC
Hu J	Non-RCT	China	/	65 (40)	84 (48)	ARB/ACEI + SOC	Non-ARB/ACEI + SOC
Fosbol E.L.	Non-RCT	Denmark	/	895 (493)	3585 (1651)	ARB/ACEI + SOC	Non-ARB/ACEI + SOC
Zhang P	Non-RCT	China	64	174 (94)	348 (197)	ARB/ACEI + SOC	Non-ARB/ACEI + SOC
Meng J	Non-RCT	China	64.5	17	25	ARB/ACEI + SOC	Non-ARB/ACEI + SOC
Li J	Non-RCT	China	66.0	115	247	ARB/ACEI + SOC	Non-ARB/ACEI + SOC
Felice C	Non-RCT	Italy	73	82 (59)	51 (27)	ARB/ACEI + SOC	Non-RAAS Inhibitor + SOC
Lopes R. D	RCT	Brazil	55.1	334 (198)	325 (195)	ARB/ACEI + SOC	Non-ARB/ACEI + SOC
Davoudi-Monfared E	RCT	Iran	/	42 (22)	39 (22)	IFN β-1a + HCQ + Lopinavir-Ritonavir/Atazanavir-Ritonavir	HCQ + Lopinavir-Ritonavir/ Atazanavir-Ritonavir
Monk P. D	RCT	U.K.	57.1	50 (31)	48 (27)	IFN β-1a + SOC	SOC
Hung I.F.	RCT	China	51.3	86 (45)	41 (23)	Lopinavir-Ritonavir + Ribavirin + Interferon beta-1b + SOC	Lopinavir-Ritonavir + SOC
Li Y	RCT	China	49.4	34 (17) / 35 (16)	17 (7)	Lopinavir-Ritonavir + SOC / Arbidol +SOC	SOC
Cao B	RCT	China	58.0	199 (120)	99 (61)	Lopinavir-Ritonavir + SOC	SOC
RECOVERY Collaborative Group	RCT	U.K.	/	1616 (973)	3424 (2104)	Lopinavir-Ritonavir + SOC	SOC
Wang Y	RCT	China	65.3	158 (89)	78 (51)	Remdesivir + SOC	Placebo + SOC
Beigel J.H.	RCT	U.S., Korea, etc.	58.9	541 (352)	522 (332)	Remdesivir + SOC	Placebo + SOC
Olender S.A.	RCT	U.S., Korea, etc.	/	312	818	Remdesivir + SOC	SOC
Spinner C.D.	RCT	U.S., U.K, etc.	/	384 (232)	200 (125)	Remdesivir + SOC	SOC
Khalili H	RCT	Iran	/	42	40	sofosbuvir/ ledipasvir +SOC	SOC
Abbaspour Kasgari H	RCT	Iran	/	24 (11)	24 (7)	Sofosbuvir + Daclatasvir + Ribavirin + SOC	SOC
Sadeghi A	RCT	Iran	58	33 (20)	33 (14)	Sofosbuvir + Daclatasvir + SOC	SOC
Ivashchenko A.A	RCT	Russia	/	40	20	Avifavir + SOC	SOC
Pan H a	RCT	U.S., U.K, etc.	/	2743 (1706)	2708 (1725)	Remdesivir + SOC	SOC
Pan H b	RCT	U.S., U.K, etc.	/	947 (574)	906 (535)	Hydroxychloroquine + SOC	SOC
Pan H c	RCT	U.S., U.K, etc.	/	1399 (851)	1372 (802)	Lopinavir + SOC	SOC
Pan H d	RCT	U.S., U.K, etc.	/	2050 (1303)	2050 (1278)	IFN β-1a + SOC	SOC
Abd-Elsalam S	RCT	Egypt	/	97 (56)	97 (58)	Hydroxychloroquine + SOC	SOC
Lyngbakken M.N.	RCT	Norway	62	27 (19)	26 (16)	Hydroxychloroquine + SOC	SOC
Boulware D.R.	RCT	U.S., Canada	40.5	414 (196)	407 (201)	Hydroxychloroquine + SOC	Placebo + SOC
Geleris J	Non-RCT	U.S.	/	811 (474)	565 (307)	Hydroxychloroquine + SOC	SOC
Gautret P	Non-RCT	France	45.1	20 (9)	16 (6)	Hydroxychloroquine + SOC	SOC
Paccoud O	Non-RCT	France	65.5	38 (21)	46 (31)	Hydroxychloroquine + SOC	SOC
Tang W	RCT	China	46.1	75 (42)	75 (40)	Hydroxychloroquine + SOC	SOC
Horby P	RCT	U.K.	/	1561 (960)	3155 (1974)	Hydroxychloroquine + SOC	SOC
Self W. H	RCT	U.S.	/	242 (135)	237 (132)	Hydroxychloroquine + SOC	Placebo + SOC

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, HCQ = hydroxychloroquine, IFN = interferon, RAAS = renin-angiotensin-aldosterone system, SOC = standard of care.

The present researches have showed different outcomes among COVID-19 medicine. For ACEI/ARB, Gao, C and colleague conducted the earliest meta-analysis combined with their research data to validate its therapeutic effect and found that ACEI/ARB could significantly reduce the mortality of COVID-19 patients.[27] However, this study revealed that ACEI/ARB hadn't significant effect in reducing mortality, demonstrating ACEI/ARB may not be the ideal medicine for COVID-19 treatment. After re-examining studies about ACEI/ARB included, data of all studies indicated ACEI/ARB had influence in mortality decrease, except for Fosbol et al.[10] Then, we looked through the full text and discovered that the patients in experimental group were more likely to have basic diseases compared to control group, which perhaps caused the higher mortality.[10] After removing this study, analysis result showed a significant decrease in mortality of COVID-19 patients (RR, 0.64; 95% confidence interval [CI], 0.48–0.85, $P < .05$). Therefore, more trials should be conducted to further evaluate the therapeutic effect of ACEI/ARB. For antiviral medicine, although quite a few controversies existed, none of study comprehensively analyzed their safety and curative effect. Therefore, we did the subgroup analysis to confirm the safety and curative effect among almost all end points. When it comes to chloroquine/hydroxychloroquine, the significant difference in therapeutic efficiency was not seen between experimental group and control group either, which is consistent with previously published studies.[52] Moreover, in spite of the significant clinical improvement in antiviral medicine, the heterogeneity still needs to be noticed. I^2 value of 70% indicated the heterogeneity existed, so we removed the studies one by one and found that after removing the study of Olenderet al,[32] the I^2 value became 0%, demonstrating this study might be the source of heterogeneity. Immediately, we made the comparison among

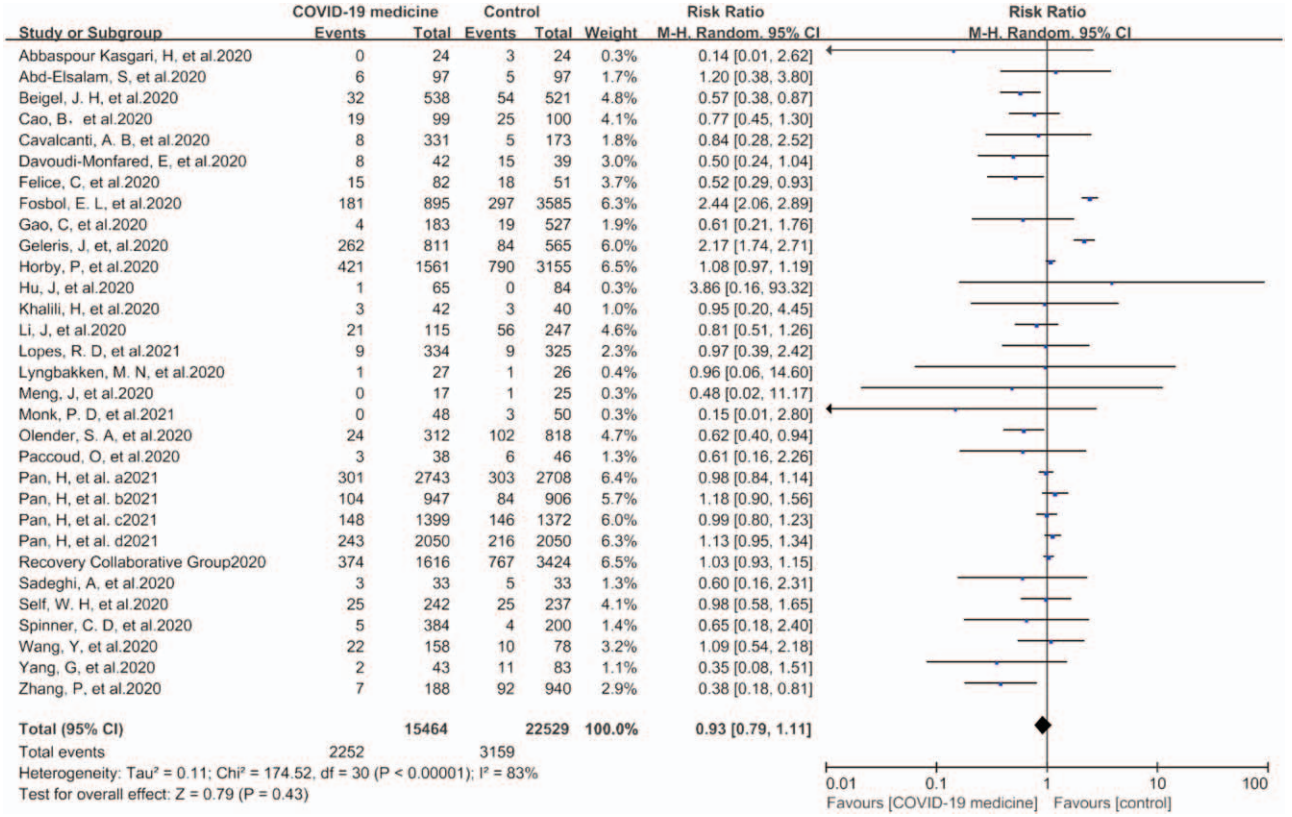

Figure 2. The mortality between COVID-19 medicine and standard treatment.

studies involved in analysis of clinical improvement rate and revealed that all studies are RCTs except for Olender et al,[32] reflecting unprecise control conditions and lack of blind method settings played the important role in heterogeneity.

It's worth noting that no drugs appeared great therapeutic effect in mortality reduction, nevertheless, antiviral medicine presented the significantly clinical improvement. In theory, ACEI/ARB inhibit the combination of angiotensin-converting enzyme 2 (ACE2), binding site of SARS-CoV-2, and SARS-CoV-2 to benefit COVID-19 patients.[53] However, it may also promote the expression of ACE2 and attenuate therapeutic effect. Besides, although chloroquine/hydroxychloroquine had considerable antiviral effect in vitro, its antiviral mechanism is still unknown. In contrast, antiviral medicine could block the proliferation of SARS-CoV-2 through different ways,[54] which is the obvious target treatment for SARS-CoV-2 theoretically. That may explain the better therapeutic effect of antiviral therapy. Nonetheless, their underlying mechanisms remain unclear, so more researches are needed to validate our hypothesis.

In terms of safety, there is still much controversy. The present study showed that the chloroquine/hydroxychloroquine has already on the market, but the clinical trials of chloroquine/hydroxychloroquine have indicated that the high doses use of it would increase the mortality as well as prolonged QT interval of COVID-19 patients' electrocardiogram,[14,55,56] which is dangerous for patients. Furthermore, compassionate use of remdesivir showed that nearly 60% COVID-19 patients had side effects.[13] Inversely, some other studies indicated COVID-19

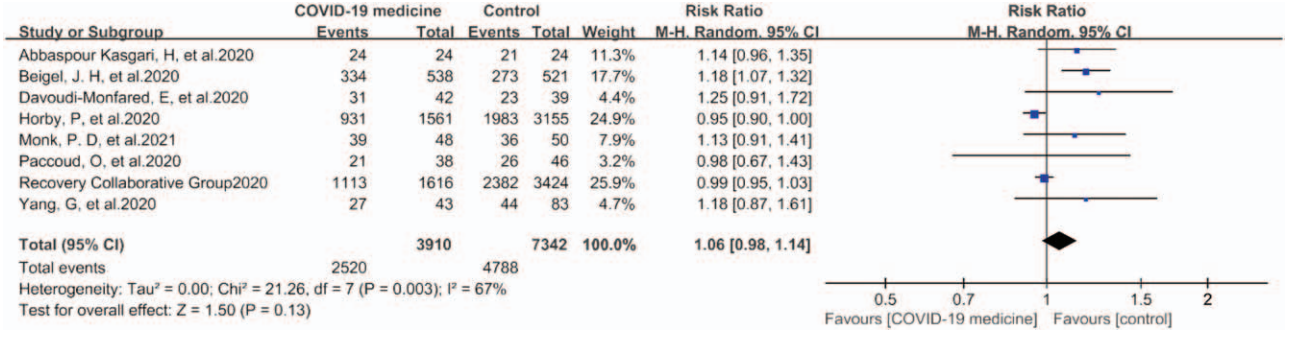

Figure 3. The discharge rate between COVID-19 medicine and standard treatment.

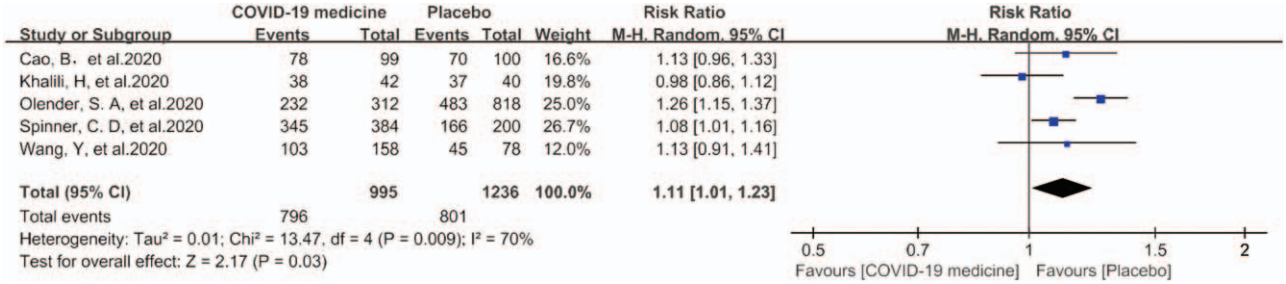

Figure 4. The clinical improvement rate between COVID-19 medicine and standard treatment.

medicine would not increase safety risk.[12,29,31] Nevertheless, this study first discussed that treating with COVID-19 medicine not only did not increase safety risks, but also decreased the rate of the serious adverse events of COVID-19 patients. The result above demonstrated that COVID-19 drug therapy was even the safer treatment than standard care. Thus, standard treatment combined with COVID-19 medicine should be recommended for COVID-19 patients' treatment.

4.1. Implications of the study

Our study has clinical implication for guiding rational drug use. On the one hand, we recommend the appropriate medicine for COVID-19 patients. Nowadays, due to the absence of effective medicine for COVID-19 patients, treatments for them are mainly symptomatic treatments.[57] In this study, antiviral medicine including remdesivir, lopinavir-ritonavir, and so on was found to have potential to improve the clinical symptom, with little adverse events, thus we advise that antiviral medicine should be adopted for priority use. In contrast, ACEI/ARB and chloroquine/hydroxychloroquine therapy do not seem to be the ideal treatments for COVID-19 therapy. In early February, chloroquine/hydroxychloroquine was reported to have apparent antiviral effect on SARS-CoV-2,[11] and then it was recommended for treatment of COVID-19 patients soon. As the clinical trials continued, chloroquine/hydroxychloroquine didn't exert the clinical effect as people expected,[36,37] thus it was gradually not recommended for use alone. We comprehensively analyzed data of the trials which used chloroquine/hydroxychloroquine and confirmed it did not reduce the mortality significantly as compared with standard care. Furthermore, although these drugs seem to have little serious adverse events, the side effects of prolonged QT interval and ventricular tachycardia should be noticed.[55,56] For those with inherent cardiovascular disease, the side effects above could significantly increase security risks. Thus, we do not recommend the treatment with chloroquine/hydroxychloroquine for COVID-19 patients, especially for those with cardiovascular disease. With regard to ACEI/ARB, the study showed that it might not have the therapeutic effect in treating COVID-19. However, in terms that the patients in experimental group in study of Fosbol et al[10] tended to have basic diseases compared to control group, confirming whether ACEI/ARB could reduce the mortality of COVID-19 patients is difficult. With the addition of safety of ACEI/ARB treatment, we suspected combination of ACEI/ARB and standard treatment play the potential role in curing COVID-19. Nonetheless, using the ACEI/ARB alone is not recommended. Thus, in the study, we draw a conclusion that antiviral medicine was probably the ideal specific medicine of COVID-19 due to its potential of clinical symptoms improvement. Chloroquine/hydroxychloroquine was not recommended for COVID-19 patients because of its safety risk and little therapeutic effect. As for ACEI/ARB, its curative effect is uncertain, thus we think combination use of ACEI/ARB and standard treatment is worthy of adopting for COVID-19 treatment. Because their therapeutic mechanisms for COVID-19 are remain unclear, and the sample size for each medicine is insufficient, more studies are needed for further confirming their efficiency and safety.

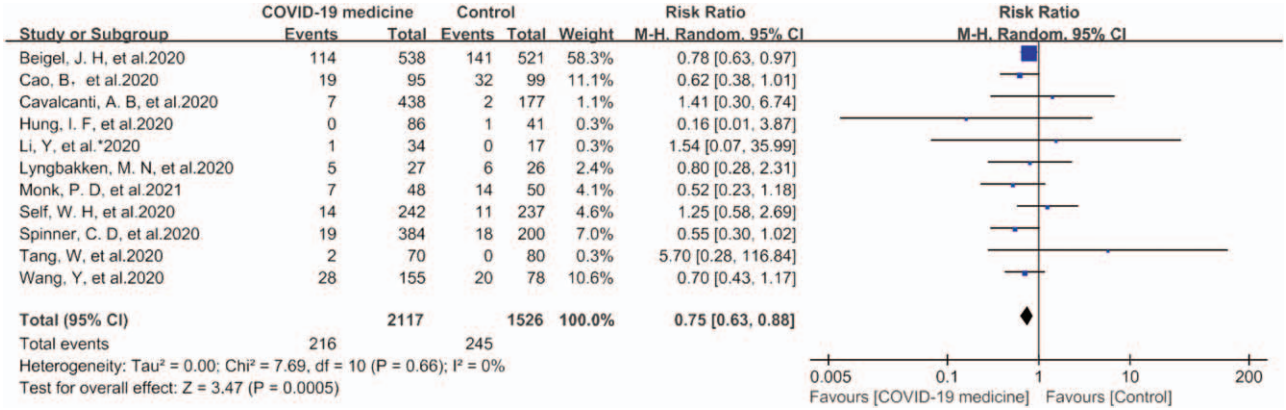

Figure 5. The rate of serious adverse events between COVID-19 medicine and standard treatment.

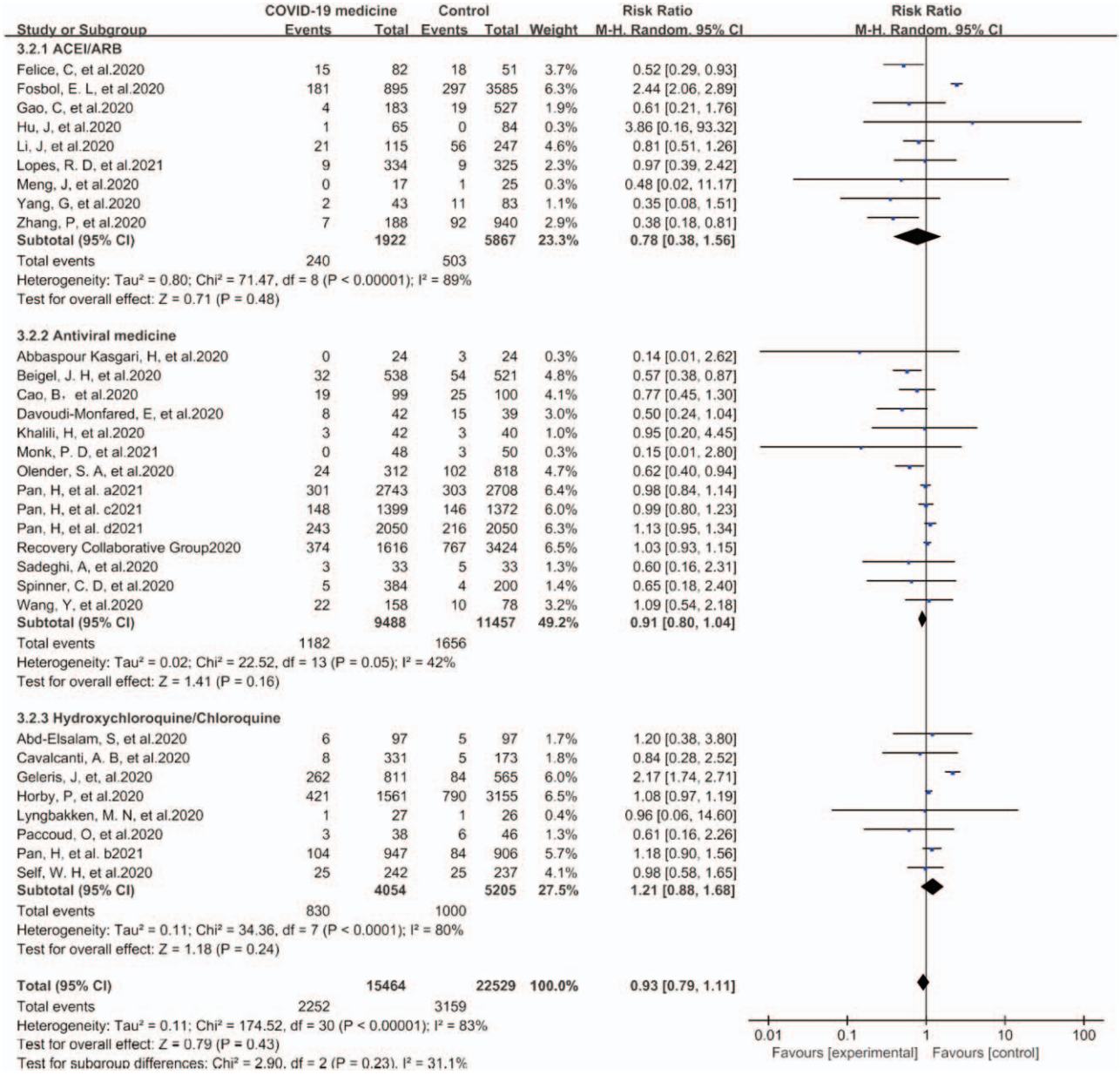

Figure 6. The subgroup analysis of mortality among different kinds of COVID-19 medicine.

4.2. Strengths and weaknesses of the study

There exist several strengths in our study. First, we are the first to evaluate the therapeutic effect and safety for the most comprehensive categories of COVID-19 medicine. The therapeutic trials of most common kinds of COVID-19 medicine, ACEI/ARB, antiviral medicine and chloroquine/hydroxychloroquine, were all included in our study. Our findings showed the significant curative effect on clinical improvement was confirmed in antiviral medicine compared to standard treatment. Currently, lack of comparison between different categories of medicine makes it difficult for clinicians to adopt appropriate medicine to treat COVID-19 patients, thus, we are also the first to do the indirect subgroup analysis among these categories of medicine and found that no medicine had the significant advantage in reducing mortality. Furthermore, the serious adverse events of COVID-19 medicine were generally lower than standard treatment, demonstrating the better safety of COVID-19 medicine. Second, the high quality of the data is another remarkable strength in this study. With the data obtained in 33 trials, we gathered more than 37,000 patients for quantitative analysis of mortality, which is the largest scale of COVID-19 patients for assessing the mortality of COVID-19 medicine up to now. Such large-scale number of patients included in our study ensured the statistical accuracy. Third, we recommended the antiviral medicine as the priority drug among COVID-19 medicine and did not support the chloroquine/hydroxychloroquine therapy, especially for patients with cardiovascular diseases. Fourth, we comprehensively look through the full text both before and after the data analysis and hypothesized that ACEI/ARB was potential specific medicines for COVID-19

patients. Although the subgroup analysis of ACEI/ARB therapy appeared that it was not associated with the mortality decrease COVID-19 patients initially, we found that one of the studies involved existed the obviously higher basic disease rate in experimental group over control group. After removing it, the result showed a reduction of mortality in ACEI/ARB compared to standard care with statistically significant P value and little heterogeneity, which is consistent with previous study.[58] Furthermore, we confirmed among ACEI/ARB, antiviral medicine, and chloroquine/hydroxychloroquine, no medicine had the obvious therapeutic effect in reducing mortality, which appeals for more effective drugs to lower the mortality rate of COVID-19 patients.

Despite the strengths above, the limitations still exist in this study. One is that the efficiency indicators aren't elaborate enough. Though we have comprehensively selected the indicators contain clinical improvement, discharge and mortality to evaluate the efficiency of COVID-19 medicine, the more precise indicators such as levels of cytokines, temperature variation and creatinine levels are impossible to obtain among most studies. Therefore, we had to assess the efficiency through these simple indicators. Another limitation is that although antiviral medicine was found to significantly improve the clinical symptoms of patients, it failed to improve the discharge rate of patients (RR, 1.11; 95% confidence interval [CI], 0.99–1.24, $P = .07$). Moreover, more studies are needed to further validate our results.

5. Conclusion

In summary, this study indicated that COVID-19 medicine had no apparent effect on mortality decrease and discharge rate increase of COVID-19 patients, but it reduced the rate of serious adverse events significantly. Furthermore, compared to standard treatment, antiviral medicine had better effect on clinical improvement, thus it had the potential to be priority drug for treatment. However, due to the insufficient quantity of trials, efficiency and safety of every single medicine cannot be evaluated in detail.

Author contributions

W. L and H. G designed this study; J. L, C. W, Y. X and Q. Z established searching strategy and collected the data; J. L and R. Q performed statistical analyses and wrote the manuscript; C. W, Z. G and Y. W assisted in the data analyses and manuscript writing. All authors looked through and agreed to the final manuscript.

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