# A systematic review and meta-analysis of Arbidol therapy for acute respiratory viral infections: A potential treatment for COVID-19

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Received June 2, 2022; Accepted September 20, 2022

DOI: 10.3892/etm.2022.11672

**Abstract.** Arbidol (ARB) is efficacious for the treatment of influenza, and has been recommended for COVID-19. The present systematic review was performed to assess the existing knowledge on ARB therapy for acute respiratory viral infections, especially COVID-19. Subsequently, six databases were searched for publications reporting clinical outcomes of ARB therapy, and registered clinical trials up to May 6, 2022. The available literature was rigorously appraised. Based on the inclusion and exclusion criteria, 20 articles were identified for the final review. The result of meta-analysis showed that there was no significant difference in the negative rate of PCR day 7 [risk ratio (RR), 1.1; 95% CI, 0.87-1.40], negative rate of PCR day 14 (RR, 1.24; 95% CI, 0.92-1.67), PCR negative conversion time [mean difference (MD), -0.26; 95% CI, -1.41-0.90], time of clinical improvement (MD, 1.11; 95% CI, 0.01-2.22), hospital stay (MD, 0.16; 95% CI, -1.62-1.93), rate of improvement on chest computed tomography (CT) (RR, 1.19; 95% CI, 0.74-1.91), duration of CT absorption (MD, -1.43; 95% CI, -10.28-7.42), disease progression (RR, 1.05; 95% CI, 0.64-1.71) and mortality (RR, 0.68; 95% CI, 0.42-1.11). ARB demonstrated significant difference in the rate of clinical improvement (RR, 0.81; 95% CI, 0.67-0.97), duration of fever (MD, -0.38; 95% CI, -0.74- -0.02) and adverse events (RR, 0.65; 95% CI, 0.45-0.94). Although past clinical studies indicates notable results of ARB on influenza, there is no consensus on the drug for therapeutic and prophylaxis of COVID-19. The safety of ARB should be carefully monitored. High quality randomized controlled studies are urgently needed to thoroughly evaluate the efficacy and safety of ARB in patients with acute respiratory viral infections, especially COVID-19.

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*Abbreviations:* COVID-19, Corona Virus Disease 2019; SARS-CoV-2, 2019 novel coronavirus; ARVI, acute respiratory viral infections; ARB, Arbidol; CT, computed tomography; HA, hemagglutinin; NOS, Newcastle-Ottawa scale; RoB, Cochrane risk of bias; RCTs, randomized controlled trials; LPV/r, lopinavir/ritonavir

*Key words:* arbidol, influenza, COVID-19, meta-analysis, efficacy

## Introduction

Acute respiratory tract infections are the third leading factor of morbidity and mortality worldwide, and constitute an enormous economic burden and public health threat worldwide (1). There are numerous and diverse viruses, which cause co-infections with other causative agents, such as fungus, atypical pathogens and other bacteria (2). Respiratory viruses are detected more frequently compared with bacteria in adults with pneumonia (3). Multiple viruses have been linked to acute respiratory viral infections (ARVI), such as influenza virus, parainfluenza viruses, respiratory syncytial virus, rhinovirus and coronaviruses (4). Influenza virus has caused several pandemics worldwide, and has become one of the most widely recognized viral infections. More recently, 2019 novel coronavirus (SARS-CoV-2) has crossed the species barrier and become a global pandemic. According to the World Health Organization report, Corona Virus Disease 2019 (COVID-19) has infected >514 million patients and resulted in >6 million deaths worldwide (as of May 6, 2022). SARS-CoV-2 can affect multiple organs, which can lead to severe disease in patients with underlying comorbidities (5). Given the rapid emergence and global spread, reducing SARS-CoV-2 infection and increasing recovery rate are critical.

Arbidol (ARB) was developed in Russia and has been used for >10 years in China for prophylaxis and treatment of influenza (6). Due to its high consumption for the prevention and treatment of COVID-19 and some other viral infections (7), it is important to reappraise the effect in reducing the risk of COVID-19 (8). As the only available antiviral drug that targets hemagglutinin (HA) (9), ARB has shown broad-spectrum antiviral activity to inhibit the replication of multiple viruses (10), and has been reported

to have preventive and therapeutic effects against influenza, COVID-19 or other ARVI (6).

ARB is recommended by Chinese guidelines (11) as a potential medication against COVID-19. ARB monotherapy or in combination with other antiviral drugs are suggested as potential strategies to combat SARS-CoV-2 (12,13). However, the effectiveness of ARB remains controversial. To the best of our knowledge, systematic reviews evaluating outcomes of clinical ARB application on ARVI are lacking. Therefore, it is important to analyze the available data on the efficacy of ARB and its therapeutic potential in COVID-19. Herein, the present study conducted a systematic review and meta-analysis of published studies and clinical trials to assess the efficacy of ARB on ARVI in order to provide guidance for the treatment of COVID-19.

## Materials and methods

*Search strategies*. The present systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses principles. The PubMed (www.ncbi.nlm.nih.gov/pubmed), MedLine, EmBase (www.embase.com), Web of Science (www.webofknowledge.com), Foreign Medical Literature Retrieval Service (FMRS) (fmrs.metstr.com) and mdRxiv (www.medrxiv.org) databases were systematically searched for relevant studies published up to May 6, 2022. Search terms used were as follows: Arbidol/umifenovir, respiratory viral infection, novel coronavirus, COVID-19, influenza, SARS (severe acute respiratory syndrome), Middle East respiratory syndrome and related words. The references of selected articles were reviewed for additional studies not retrieved by the initial search.

*Inclusion and exclusion criteria*. Studies conducted in humans describing the impact of ARB treatment against RVI were included. *In vitro* and animal studies, articles written in languages other than English, review articles and studies focused on the mechanism of action of drugs were excluded. Two investigators (JY and HD) independently screened and extracted the relevant data from the included studies.

*Data extraction*. Information from selected studies was extracted and tabulated. The extracted data included the first author, year of publication, country, study type, characteristics of patients, treatment plan and outcomes. The primary outcomes included PCR negative rate on day 7 and 14, PCR negative conversion time, rate of clinical improvement, time of clinical improvement, rate of chest computed tomography (CT) absorption and duration of chest CT absorption. The secondary outcomes included hospital length of stay, duration of fever, rate of disease progression, adverse events and mortality.

*Risk of bias assessment*. Two investigators (YS and XZ) independently assessed the risks of bias in each included study. For observational studies the Newcastle-Ottawa scale (NOS) (14) was used, which consists of three domains: Selection, comparability and outcome. NOS scores of 1-4, 5-7 and 8-9 indicated low, moderate and high quality. Generally, studies which earned ≥five points were included in the final analysis. For randomized controlled trials (RCTs), the Cochrane risk of bias (RoB) tool (15) was used, which consists of five domains: Selection bias, performance bias, attrition bias, reporting bias and other biases. The potential bias was graded as low, unclear or high.

*Statistical analysis*. The analysis was conducted using the Review Manager software (version 5.4; Cochrane) (https://training.cochrane.org/online-learning/core-software/revman). Mean difference (MD) was used for continuous outcomes, and risk ratio (RR) was used for dichotomous variables. A 95% confidence interval (CI) was calculated for each study. Statistical heterogeneity was evaluated using the I-square and $\chi^2$ tests, where I-square >50% or P<0.10 were considered to indicate a statistically significant difference. The random-effects model was used for studies with significant heterogeneity. Otherwise, the fixed-effect model was used. Sensitivity analyses was performed manually by single study elimination method in Review Manager 5.4 software to verify conclusions of meta-analysis and explore the possible reasons of heterogeneity. Publication bias was evaluated using funnel plots. Review Manager software (version 5.3; Cochrane) was used to statistically analyze all of the data.

## Results

*Search results*. A total of 1,529 articles were retrieved from the initial search of databases. Of those, 1,500 articles were excluded due to the following reasons: Duplicates (n=873), review articles (n=176), *in vitro* and animal studies (n=214), pharmacology (n=197), unrelated to ARB (n=32) and were not written in the English language (n=9) or describe the treatment (n=8). Therefore, only 20 articles (16-36) eventually met the inclusion and exclusion criteria, and were included in the final analysis (Fig. 1). Overall, one study reported therapeutic effect among patients with influenza during epidemic period, while 19 studies reported on the therapeutic and prophylaxis effect among patients with COVID-19. Characteristics of the 20 studies included in the present review are summarized in Table I. Assessment of quality of the results of RoB and NOS were presented in Table I and Fig. 2. More than half of the observational studies (n=10) were moderate quality, the main reasons were being the lack of ascertainment of exposure and adequacy of follow up of cohorts. The other six studies were high quality (n=6). All of the included four RCTs had a low risk of bias for random sequence generation. With regard to other risk of bias, in the study by Chang *et al* (20), the staff knew the patient grouping and did not acquire complete outcome data; therefore, the high risk of bias was due to allocation concealment, insufficient blinding, incomplete outcome and selective reporting.

*Efficacy of ARB in influenza*. According to the inclusion and exclusion criteria, there was only one article among patients with influenza or acute respiratory tract infection that was included in the final study. In the retrospective study performed on 442 patients with influenza (16), the patients treated with oseltamivir or ARB had significantly lower chances (0 and 0.3%, respectively) of developing pneumonia compared with patients who did not receive antiviral therapy (23.7%; P<0.001).

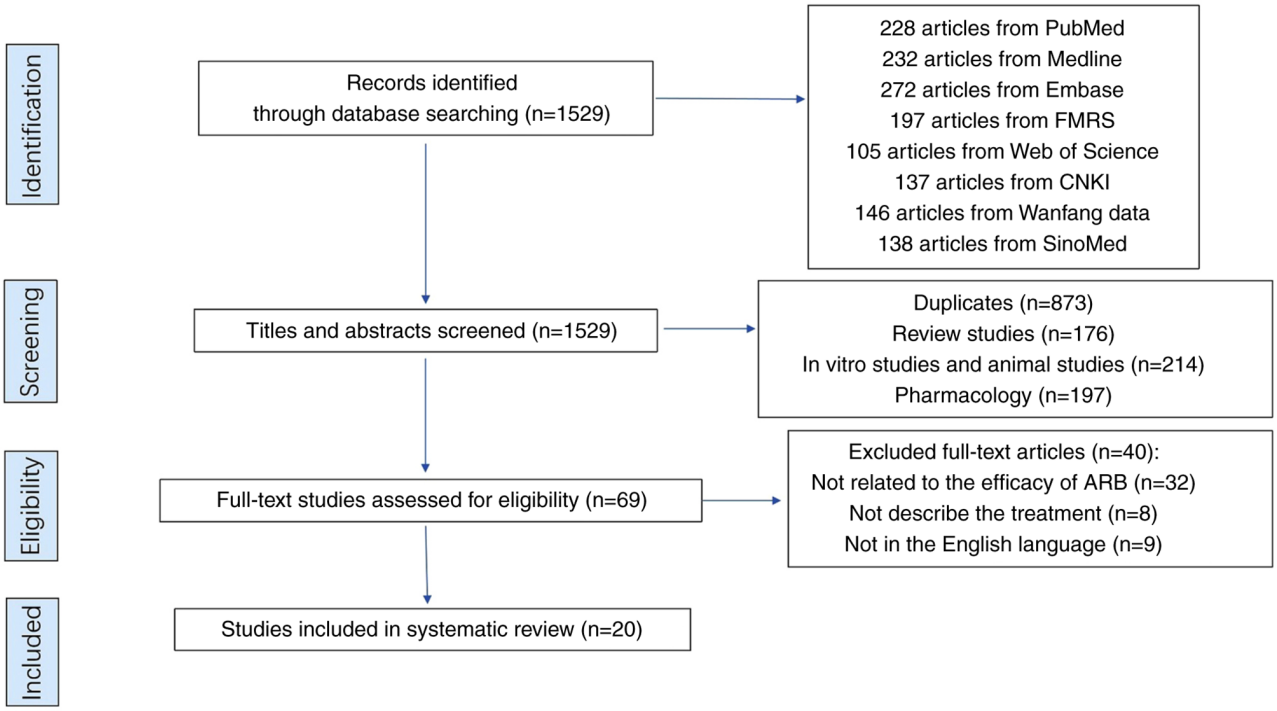


Figure 1. Flow diagram of the number of studies screened and included in the systematic review.

*Therapeutic effects of ARB in COVID-19*. Numerous studies have been conducted on ARB effect against COVID-19. The 17 available (17-34) articles were mostly from China. A total of four RCTs and 13 observational studies reported clinical outcome data of therapeutic effects on ARB treatment. Overall, sixteen studies were from China and one study was from Iran.

*The PCR negative conversion*. There were 4 and 6 studies that reported PCR negative rate on days 7 and 14, respectively. As depicted in Fig. 3, ARB was not significantly associated with higher negative rate of PCR on day 7 (RR, 1.1; 95% CI, 0.87-1.40; Fig. 3A) and day 14 (RR, 1.24; 95% CI, 0.92-1.67; Fig. 3B). A total of seven studies reported PCR negative conversion time. No significant difference was observed for PCR negative conversion time (MD, -0.26; 95% CI, -1.41-0.90; Fig. 3C).

*Main symptom improvement*. There were three studies that reported the rate and time of clinical improvement, respectively. ARB demonstrated significant difference in the rate of clinical improvement (RR, 0.81; 95% CI, 0.67-0.97; Fig. 4A), but this difference was not significant in the time of clinical improvement (MD, 1.11; 95% CI, 0.01-2.22; Fig. 4B). A total of seven studies reported the duration of fever that is the most representative main symptom of COVID-19. ARB was associated with shorter duration of fever (MD, -0.38; 95% CI, -0.74- -0.02; Fig. 4C). In addition, five studies reported the hospital length of stay. ARB showed no significant difference in terms of hospital stay (MD, 0.16; 95% CI, -1.62-1.93; Fig. 4D).

*Chest CT absorption*. There were four and two studies that reported the rate and duration of chest CT absorption, respectively. No significant difference was observed between ARB and non-ARB group in rate of improvement on chest CT (RR, 1.19; 95% CI, 0.74-1.91; Fig. 5A) and duration of CT absorption (MD, -1.43; 95% CI, -10.28-7.42; Fig. 5B).

*Preventive effects of ARB*. In addition to therapeutic effect, clinical studies recommended ARB for prophylaxis. The two studies (35,36) reported prophylaxis effects on ARB treatment. The retrospective study, conducted on 66 family members and 126 healthcare workers who were exposed to confirmed patients with COVID-19, revealed that ARB post-exposure prophylaxis was a protective factor against the development of COVID-19 ($P<0.01$) (35). Another study (36) reported that the cumulative uninfected rate of healthcare professionals in the ARB group was significantly higher compared with that of individuals in the non-ARB group; and the hospitalization rate was significantly associated with age and oral ARB administration.

*Safety of ARB*. There were eight and five studies that reported the rate of disease progression and mortality, respectively. As shown in Fig. 6, no significant difference was observed in terms of disease progression (RR, 1.05; 95% CI, 0.64-1.71; Fig. 6A) and mortality (RR, 0.68; 95% CI, 0.42-1.11; Fig. 6B). A total of four studies reported the adverse events. ARB showed significant difference in terms of adverse events (RR, 0.65; 95% CI, 0.45-0.94; Fig. 6C).

*Publication bias and sensitivity analysis*. Given that only a few studies ($n<10$) were included in each outcome, funnel plots to evaluate publication bias might have limited. Thus, publication bias was not analyzed further. For outcomes with high heterogeneity, sensitivity analysis was performed to verify conclusions of meta-analysis. After excluding each

Table I. Characteristics of studies included in the systematic review.

Observational studies

| Author, year | Country | Patients | Treatment plan | Primary outcome | NOS | (Refs.) |
|---|---|---|---|---|---|---|
| Leneva IA, 2016 | Russia | 442 patients with influenza | Early antiviral treatment:<br>55 patients: ARB (200 mg, qid, po) for 5 days<br>55 patients: Oseltamivir (75 mg, bid, po) for 5 days<br>252 patients: Late antiviral treatment<br>48 patients: No antiviral treatment | The overall illness duration<br>Duration of main symptoms, including fever and catarrhal symptoms | 6 | (16) |
| Zhu Z, 2020 | China | 50 patients with COVID-19 | 34 patients: LPV/r (400 mg/100mg, bid, po) for a week<br>16 patients: ARB (0.2 g, tid, po) | Duration of fever<br>PCR negative conversion time | 7 | (17) |
| Li M, 2021 | China | 62 patients with COVID-19 | 42 patients: ARB 0.2 g tid po for 10 days<br>20 patients: Chloroquine 500 mg bid for 10 days | The PCR negative rates<br>The length of hospital stay | 8 | (18) |
| Wang ZL, 2020 | China | 69 patients with COVID-19 | 36 patients: ARB (0.4 g, tid, po) for 9 days (median).<br>33 patients: Placebo | Discharge rate<br>Mortality | 6 | (21) |
| Chen W, 2020 | China | 62 patients with COVID-19 | 42 patients: ARB (0.2 g, tid, po) + symptomatic treatment<br>20 patients: Symptomatic treatment | The main symptom improvement<br>The PCR negative conversion time<br>Duration of fever<br>The length of hospital stay | 6 | (23) |
| Jie X, 2021 | China | 252 patients with COVID-19 | 228 patients: ARB 200 mg tid po<br>24 patients: Did not use ARB | The rate of clinical improvement | 8 | (24) |
| Gao W, 2020 | China | 220 patients with COVID-19 | 90 patients: ARB 200 mg tid po for 4-8 days<br>40 patients: ARB and other antiviral drugs<br>45 patients: No antiviral drugs<br>45 patients: Other antiviral drugs | The main symptom improvement<br>The length of hospital stay<br>The PCR negative rates | 8 | (25) |
| Chen N, 2021 | China | 140 patients with COVID-19 | 79 patients: ARB 0.2 g tid po for 7-10 days<br>61 patients: Did not use ARB | Duration of fever<br>The PCR negative rates<br>The PCR negative conversion time<br>The main symptom improvement | 6 | (26) |
| Deng L, 2020 | China | 33 patients with COVID-19 | 16 patients: ARB (200 mg, q8h, po) + LPV/r (400 mg/100 mg, q12h, po);<br>17 patients: LPV/r (400 mg/100 mg, q12h, po);<br>All patients received supportive therapy | The PCR negative rates<br>The rates of improvement of chest CT | 9 | (27) |
| Xu P, 2020 | China | 141 patients with COVID-19 | 71 patients: ARB (200 mg, po, tid for 7-10 days) + IFN-α2b<br>70 patients: IFN-α2b inhale, bid for 10-14 days) | The PCR negative conversion time<br>The main symptom improvement<br>Duration of CT absorption<br>Duration of fever | 7 | (28) |

Table I. Continued.

| Observational studies | | | | | | |
|---|---|---|---|---|---|---|
| Author, year | Country | Patients | Treatment plan | Primary outcome | NOS | (Refs.) |
| Wei S, 2021 | China | 132 patients with COVID-19 | 72 patients: ARB 200 mg tid po for 10 days<br>82 patients: Did not use ARB | The PCR negative conversion time<br>Duration of CT absorption | 5 | (29) |
| Lian N, 2020 | China | 81 patients with COVID-19 | 45 patients: ARB (0.2 g, tid, po)<br>36 patients: Control | Hospital length of stay<br>The PCR negative rates<br>The PCR negative conversion time | 7 | (30) |
| Lan X, 2020 | China | 73 patients with COVID-19 | 34 cases: LPV/r 400 mg/100 mg, bid<br>39 cases: LPV/r 400 mg/100 mg bid + ARB 200 mg tid | Hospital length of stay<br>Duration of fever<br>The PCR negative rates<br>The rate of disease progression<br>Mortality<br>The main symptom improvement<br>Duration of CT absorption | 8 | (33) |
| Chen X, 2020 | China | 280 patients with COVID-19 | 37 patients: ARB<br>121 patients: Did not use antiviral<br>17 patients: Chloroquine<br>13 patients: Oseltamivir<br>60 patients: LPv/r<br>16 patients: Lpv/r + ARB<br>5 patients: Chloroquine + ARB<br>11 patients: Oseltamivir + ARB | Hospital length of stay<br>The PCR negative conversion time | 9 | (34) |
| Zhang JN, 2020 | China | 66 family members and 124 health care workers had close exposure with COVID-19 patients | 1st cohort:<br>45 family members: ARB PEP (0.2 g, po, tid for 5-14 days)<br>21 family members: Did not use ARB<br>2nd cohort:<br>55 health care workers: ARB PEP (0.2 g, po, tid for 5-14 days)<br>69 health care workers: did not use ARB | The infection risk of the novel coronavirus in hospital and family settings | 7 | (35) |
| Yang C, 2020 | China | 82 patients with COVID-19 | 82 cases: Infected group<br>19 patients: ARB 600 mg qd po<br>82 cases: Uninfected group<br>48 patients: ARB 200 mg qd po | The cumulative uninfected rate<br>The hospitalization rate | 6 | (36) |

Table I. Continued.

B, Randomized controlled trials

| Author, year | Country | Patients | Treatment plan | Primary outcome | NOS | (Refs.) |
|---|---|---|---|---|---|---|
| Nojomi M, 2020 | China | 100 patients with COVID-19 | 50 cases: Hydroxychloroquine (400 mg bid) on first day followed by LPV/r bid<br>50 cases: Hydroxychloroquine (400 mg bid) on first day followed by ARB (200 mg tid) | The PCR negative conversion time<br>The length of hospital stay<br>Duration of fever<br>Duration of CT absorption<br>Mortality | RoB | (19) |
| Chang C, 2020 | China | 240 patients with COVID-19 | 120 patients: ARB (200 mg tid)<br>120 patients: Favipiravir (1,600 mg bid first day followed by 600 mg bid) for 10 days | The rate of clinical improvement<br>The rate of disease progression<br>Mortality | RoB | (20) |
| Alavi DI, 2021 | Iran | 101 patients with COVID-19 | 51 patients: LPV/r (400 mg/100 mg bid for 10-14 days) + hydroxychloroquine (400 mg single dose) + IFNβ1a (Subcutaneous injections of 44 $\mu$g (12,000 IU) on days 1, 3, 5) + ARB (200 mg tid for 10 days)<br>50 patients: LPV/r (same dose) + hydroxychloroquine (same dose) + IFNβ1a (same dose) | Hospital length of stay<br>The rate of disease progression<br>Mortality<br>The main symptom improvement | RoB | (22) |
| Li Y, 2020 | China | 86 patients with COVID-19 | 34 patients: LPV/r 400/100 mg bid po for 7-14d<br>35 patients: ARB 200 mg tid po for 7-14d<br>17 patients: No antiviral therapy | The PCR negative rates<br>The PCR negative conversion time<br>The rate of disease progression<br>The main symptom improvement<br>Duration of CT absorption | RoB | (32) |

ARB, arbidol; NOS, Newcastle-Ottawa scale; RoB, Cochrane risk of bias; ARVI, acute respiratory viral infections; IFN-α2b, Interferon alfa-2b; LPV/r, lopinavir/ritonavir; CRP, C-reactive protein; PCT, procalcitonin; CT, computed tomography; PCR, polymerase chain reaction; AOT, auxiliary oxygen therapy; NMV, non-invasive mechanical ventilation; po, per os; qd, once a day; bid, twice a day; tid, three times a day; qid, four times a day; q8h, every 8 h; q12h, every 12 h; tiw, three times a week; PEP, post-exposure prophylaxis.

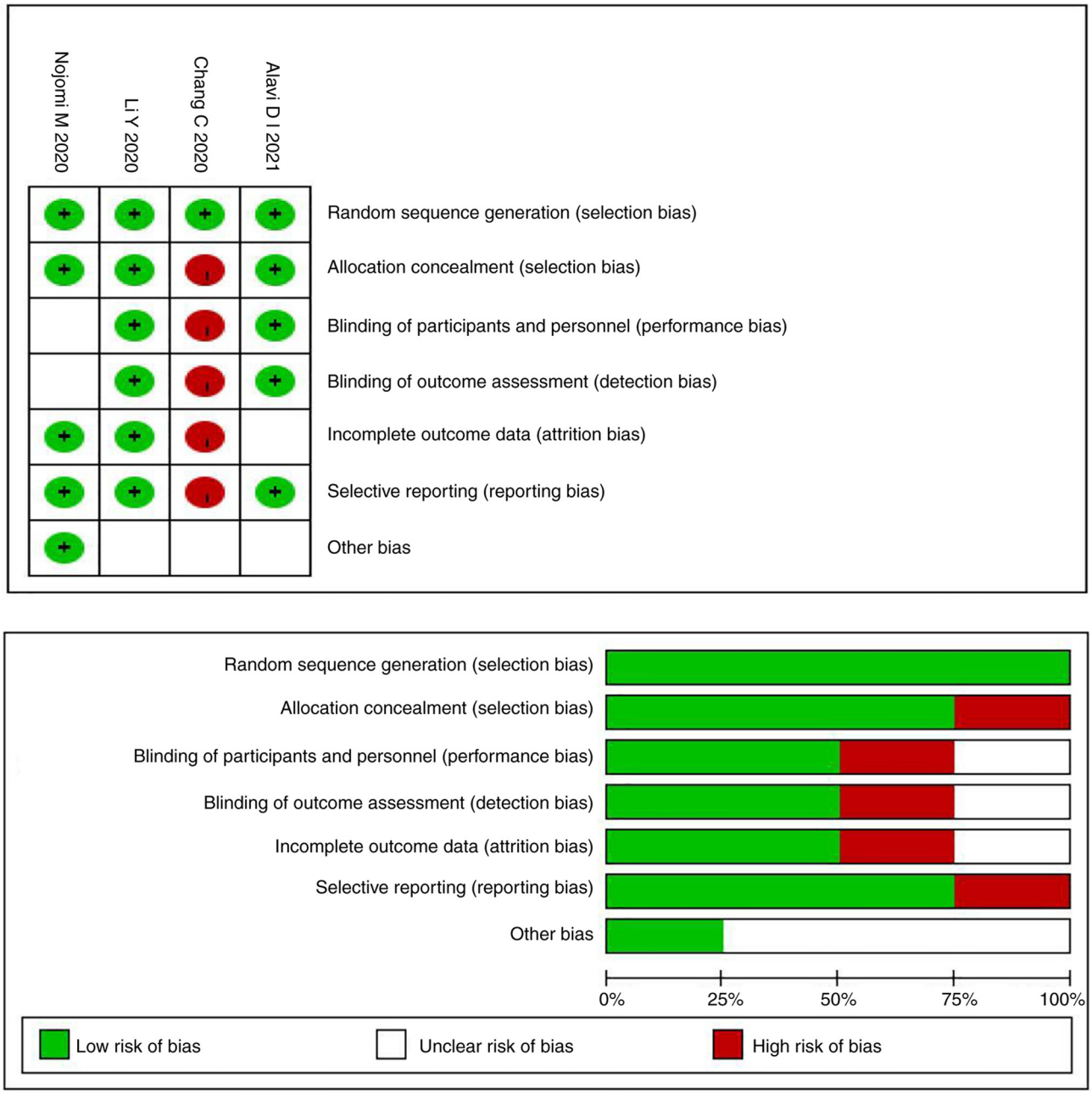


Figure 2. Analysis of risk of bias in the selected studies.

single study, sensitivity analysis had similar results ($I^2$ 67-91%; P>0.05) which did not change the significance in outcomes. Generally, the conclusion of the present study was relatively stable.

## Discussion

The present study described and summarized the available published literature on the outcomes of ARB on ARVI. Although ARB has shown inhibitory activity against various viruses, evidence for clinical beneficial effects on ARVI mainly focused on patients suffering from influenza or COVID-19 (6). The present study reviewed current clinical studies on ARB and discussed whether patients would benefit from this antiviral drug.

Since the emergence of the COVID-19 pandemic, the antiviral treatments remain limited. Some FDA-approved drugs (even originally non-antiviral) could have a potential benefit against SARS-CoV-2. Jeon *et al* (37) and Weston *et al* (38) reported >20 potential antiviral drug candidates inhibit SARS-CoV-2 *in vitro*. An RCT (39) that enrolled 379 patients with severe COVID-19 revealed that hydrocortisone has a 80-93% probability of superiority compared with no hydrocortisone. Some other drugs (Favipiravir, Remedsivir) have also been recommended, although there is insufficient evidence to support their effectiveness (40). Repurposing and reappraising existing antiviral drugs is the most appropriate recommendation, which deserves further consideration. ARB has improved efficacy and advantages over other commonly used antiviral drugs. M2 ion channel blockers (amantadine

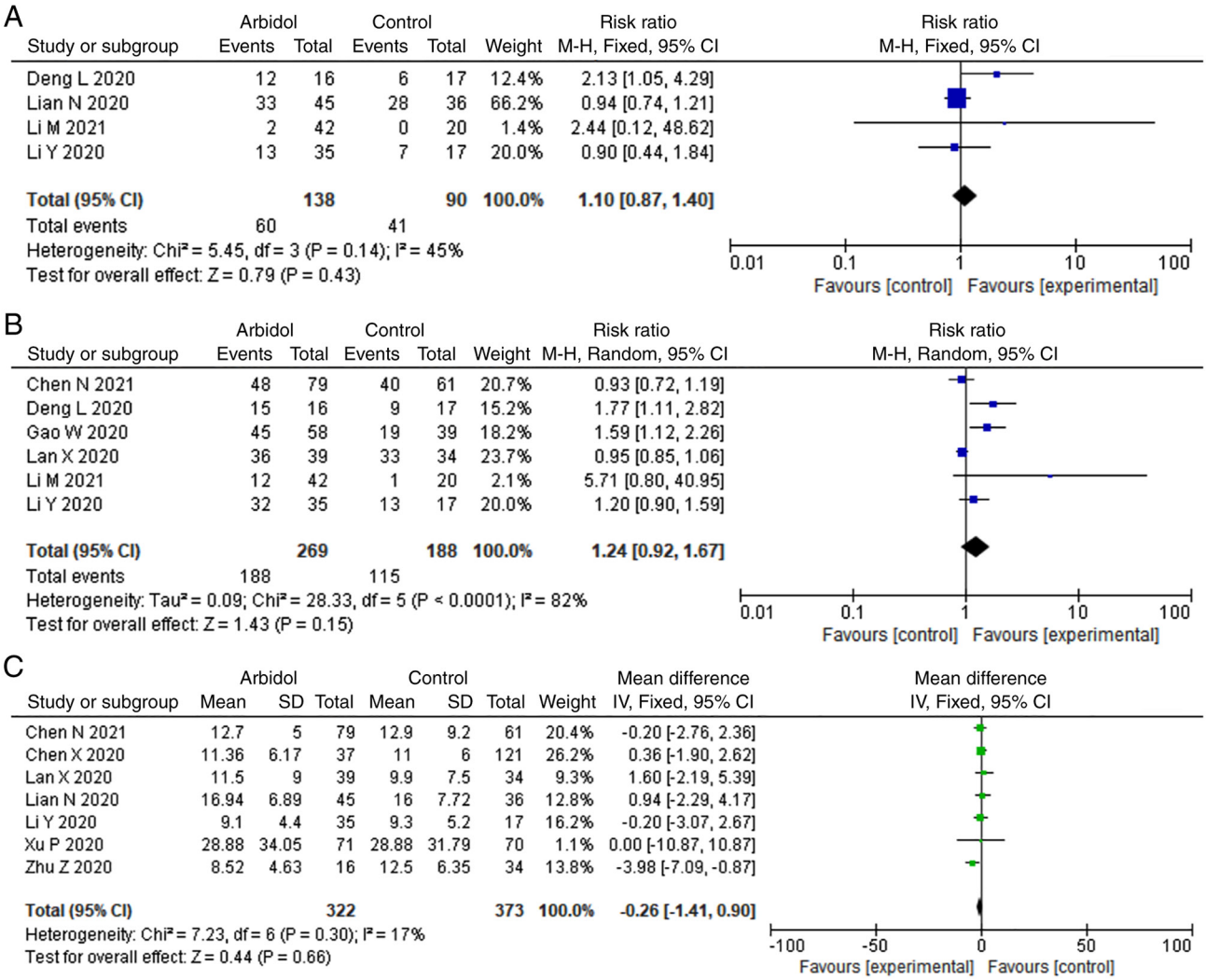


Figure 3. Forest plot of arbidol vs. control for outcomes of negative rate of PCR on (A) day 7 and (B) day 14, and (C) PCR negative conversion time.

and rimantadine) may lead to significant adverse events, and are not recommended for treating influenza due to drug resistance (41). Neuraminidase inhibitors (NA) (zanamivir and oseltamivir) are more expensive compared with ARB (42) and ineffective in inhibiting SARS-CoV-2 (41). Given the shortcomings of these currently approved compounds and the potential risk of antiviral resistance, there is an urgent need for developing new antiviral drugs (43). Leneva *et al* (16) reported that both ARB and oseltamivir are efficient at reducing the duration of overall illness and main influenza symptoms. Another study performed on patients diagnosed with COVID-19 (17) suggested that ARB monotherapy may be superior to lopinavir/ritonavir (LPV/r). Therefore, ARB could be a suitable candidate to combat COVID-19 and other respiratory viral infections.

The majority of studies have revealed that ARB possesses a dual pharmacological action, specific antiviral effect and anti-inflammatory efficacy (6,44,45). ARB has been regarded as the pioneer of HA-targeted drugs. By inhibiting HA located on the surface of influenza virus, ARB can specifically inhibit virus attachment to host cells, and block viral fusion and viral replication. A recent study (10) demonstrated sequence and structural similarities between influenza virus (H3N2) HA protein and SARS-CoV-2 spike glycoprotein, which indicates how the influenza virus drug ARB can be a potential drug for SARS-CoV-2 infections. Another study (41) also revealed that ARB interferes with SARS-CoV-2 binding and intracellular vesicle trafficking. In addition, ARB inhibits the release of several pro-inflammatory cytokines (IL-6, IL-8, IL-10 and TNF-a) in serum induced by influenza (46). The inhibitory effect of ARB on sudden cytokine storm in patients with COVID-19 has also been suggested (47). Furthermore, ARB can influence non-specific defense factors, induce interferon and specifically activate phagocytes (48). A study based on the dual pharmacological action, ARB could therefore constitute an alternative drug for the prophylaxis and treatment of influenza, COVID-19 and other respiratory viruses.

In the present study, available clinical data on the use of ARB against SARS-CoV-2 were collected from limited studies. The majority of studies reported that ARB treatment shows a tendency to minimize the duration of symptoms, diminish SARS-CoV-2 replication, decrease the mortality rate and improve the discharge rate (21,23,27). Seasonal and post-exposure prophylaxis with ARB can reduce the infection risk of SARS-CoV-2 and significantly prevent transmission (35). Yang *et al* (36) also concluded that prophylactic oral ARB is

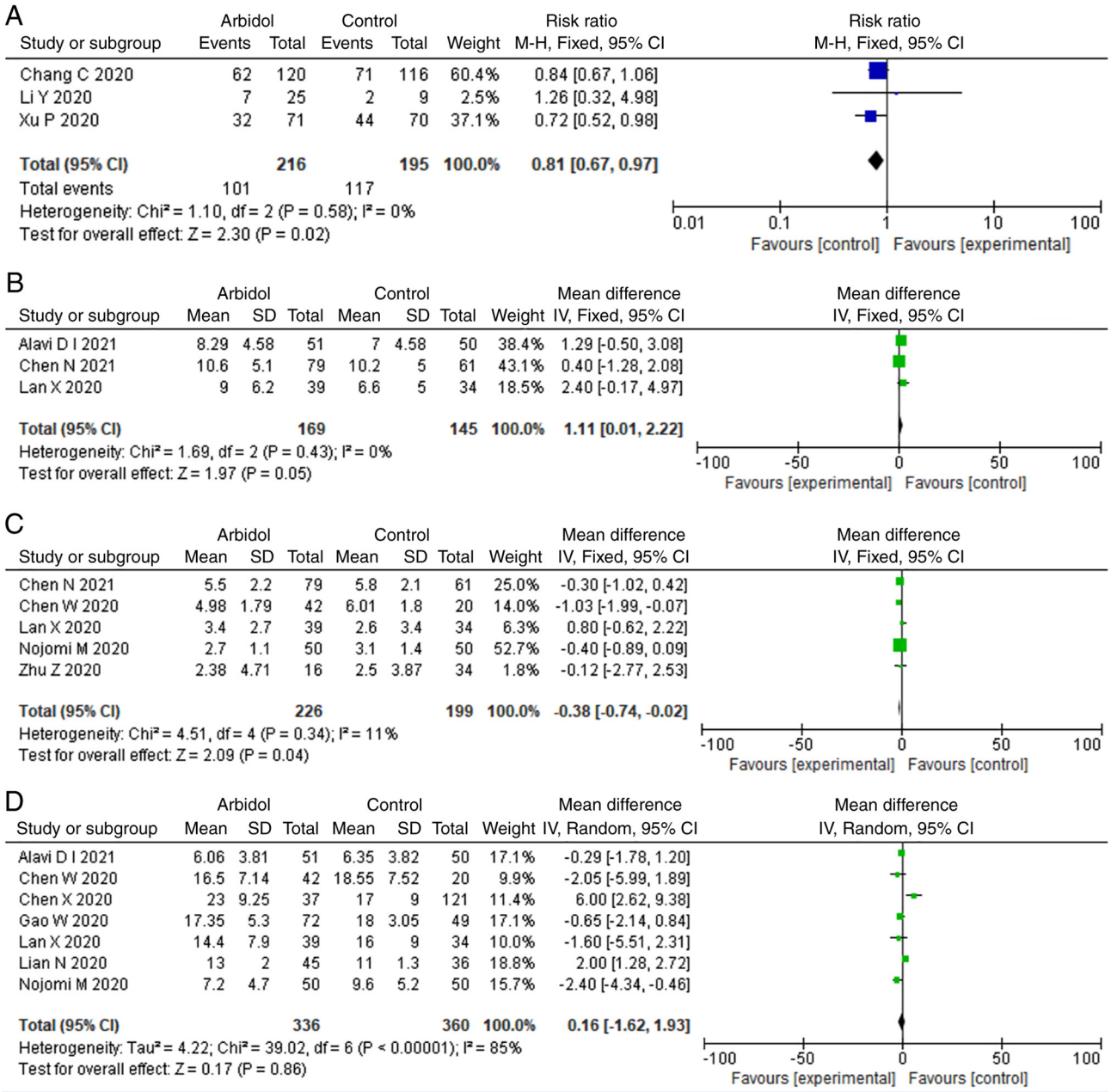


Figure 4. Forest plot of arbidol vs. control for outcomes of (A) rate of clinical improvement, (B) time to clinical improvement, (C) duration of fever and (D) hospital stay.

associated with a lower incidence of SARS-CoV-2 infection but not hospitalization rate among healthcare professionals. Although the treatment of ARB alone may be beneficial for numerous viral infections, combination therapy with other drugs with different antiviral mechanisms and resistance profiles may be able to produce the desired results in the fight against COVID-19 (49). The most commonly used combination is ARB and LPV/r. Two studies (23,27) have demonstrated that patients with COVID-19 show significant improvement in pneumonia-associated symptoms and apparent favorable clinical response with ARB+LPV/r. Another study (28) infers that ARB+IFN-2b therapy can be used as an effective method to improve COVID-19 pneumonia of mild patients, although it could not accelerate viral clearance. Hence, ARB may show an improved efficacy if combined with other antiviral drugs. However, ARB effect on COVID-19 remains controversial. Several studies (30,32) infer that ARB presents little benefit for improving the symptoms of patients or reducing the negative conversion time of SARS-CoV-2 nucleic acid. Furthermore, a timely initiation of antiviral treatment is likely an important factor that may be able to influence the prognosis of ARVI (50). Early antiviral treatment within 48 h of symptom onset shows a shorter overall illness compared with delayed antiviral treatment (16). Another study also found that early prescription of ARB in the acute stage of influenza can majorly reduce the duration, severity of all symptoms and minimize the risk of development of complications (35).

ARB is well tolerated and safe in the treatment of influenza, COVID-19 and other ARVI (51). Most studies did not find apparent side effects in the ARB treatment group (30,31).

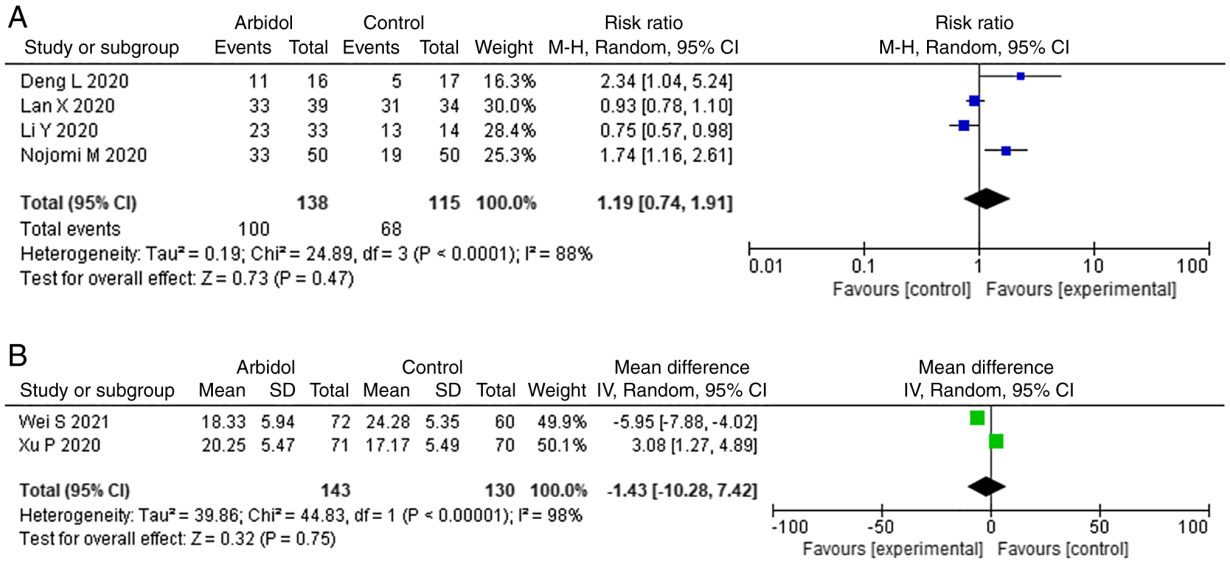


Figure 5. Forest plot of arbidol vs. control for outcomes of (A) rate and (B) duration of CT absorption.

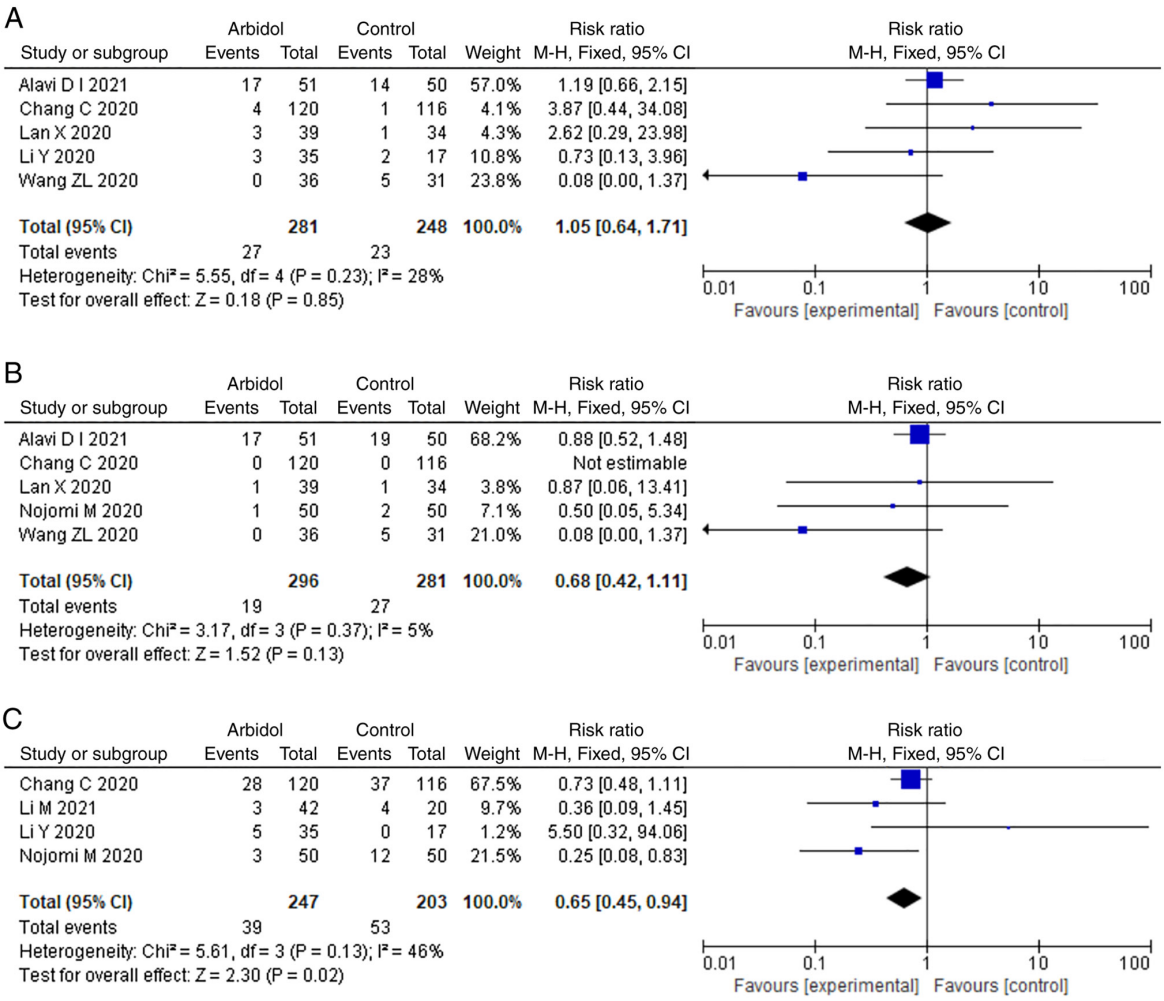


Figure 6. Forest plot of arbidol vs. control for outcomes of (A) disease progression, (B) mortality and (C) adverse events.

The adverse events reported were gastrointestinal symptoms, increased transaminase, moderate thirst and less sleep (23). Xu *et al* (28) reported that 18.8% of patients treated with ARB demonstrate mild nausea and stomachache, but all patients can tolerate this without giving up treatment. However, not all studies have arrived at a consistent conclusion on ARB safety.

Deng *et al* (27) observed that 68.7% of patients demonstrate elevated levels of bilirubin and 43.7% patients demonstrate digestive issues, such as mild diarrhea and nausea (P>0.05), but no premature discontinuation secondary to adverse effects was observed. Jiang *et al* (52) demonstrated that LPV/r can significantly inhibit the metabolism of ARB, hence the combination treatment of LPV/r and ARB was an independent risk factor for liver injury. Another study (28) revealed that adverse reactions occur more frequently in groups receiving LPV/r or ARB compared with the control group (P<0.05). Therefore, the adverse reactions of the antiviral medication should be carefully monitored.

The present review aimed to summarize all relevant published clinical data updated until May 6, 2022. The results suggested significant potential for using ARB in the prophylaxis and treatment of influenza and the target of future COVID-19 studies. However, available clinical data on the ARB treatment for COVID-19 comes from limited studies. The designs of the observational studies were inconclusive; the RCT data was lacking, and the quality evidence of the case series reports was very low. These studies were heterogeneous and thus a definitive conclusion that ARB was beneficial against COVID-19 could not be established. Many of the patients underwent multiple concurrent and comprehensive treatments; so it is not known whether the clinical benefit was from ARB or other treatments.

In summary, the HA inhibitor ARB has been extensively used to combat influenza. Potential associations were investigated, and the majority of studies reported ARB efficacy. Based on the experience from influenza therapy, ARB could be a potential treatment for SARS-CoV-2. However, there is no consensus on the ARB therapy in ARVI caused by coronaviruses. It is still uncertain whether ARB improves clinical outcomes of COVID-19. Hence, repurposing existing antiviral drugs against COVID-19 deserves further evaluation and clinical verification. High quality evidence is needed to assess the benefits of ARB in treating COVID-19 to improve clinical and programmatic decisions.

**Acknowledgements**

Not applicable.

**Funding**

This study was supported by Science and Technology Planning Project of Sichuan Province (grant no. 2019YFS0309) and Cadre Health Care Project of Sichuan Province (grant no. 2018-224).

**Availability of data and materials**

All data generated and/or analyzed during this study are included in this published article.

**Authors' contributions**

TF, JG and RT were involved in the design, analysis and manuscript writing. YS and XZ performed statistical analysis and assessed the quality of the study. JY and HD extracted and analyzed the data. TF and RT confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Welte T and Köhnlein T: Global and local epidemiology of community-acquired pneumonia: The experience of the CAPNETZ network. Semin Respir Crit Care Med 30: 127-135, 2009.
2. Zhu YG, Tang XD, Lu YT, Zhang J and Qu JM: Contemporary situation of community-acquired pneumonia in China: A systematic review. J Transl Int Med 6: 26-31, 2018.
3. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM, *et al*: Community-acquired pneumonia requiring hospitalization among U.S. Adults. N Engl J Med 373: 415-427, 2015.
4. Shi T, Arnott A, Semogas I, Falsey AR, Openshaw P, Wedzicha JA, Campbell H, Nair H and Investigators R: The etiological role of common respiratory viruses in acute respiratory infections in older adults: A systematic review and meta-analysis. J Infect Dis 222: S563-S569, 2020.
5. Armentano GM and Carneiro-Ramos MS: Effect of COVID-19 on cardiorenal axis: Known or unknown universe? Braz J Med Biol Res 55: e11932, 2022.
6. Blaising J, Polyak SJ and Pécheur EI: Arbidol as a broad-spectrum antiviral: An update. Antiviral Res 107: 84-94, 2014.
7. Ul'yanovskii NV, Kosyakov DS, Sypalov SA, Varsegov IS, Shavrina IS and Lebedev AT: Antiviral drug Umifenovir (Arbidol) in municipal wastewater during the COVID-19 pandemic: Estimated levels and transformation. Sci Total Environ 805: 150380, 2022.
8. McKee DL, Sternberg A, Stange U, Laufer S and Naujokat C: Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacol Res 157: 104859, 2020.
9. Kadam RU and Wilson IA: Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc Natl Acad Sci USA 114: 206-214, 2017.
10. Vankadari N: Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein. Int J Antimicrob Agents 56: 105998, 2020.
11. National Health Commission of the People's Republic of China. Diagnosis and treatment plan for COVID-19 (trial version 8 revision). Chin J Clin Infect Dis 14: 81-88, 2021.
12. Abdelrahman Z, Liu Q, Jiang S, Li M, Sun Q, Zhang Y and Wang X: Evaluation of the current therapeutic approaches for COVID-19: A systematic review and a meta-analysis. Front Pharmacol 12: 607408, 2021.
13. Jomah S, Asdaq SMB and Al-Yamani MJ: Clinical efficacy of antivirals against novel coronavirus (COVID-19): A review. J Infect Public Health 13: 1187-1195, 2020.
14. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25: 603-605, 2010.
15. Higgins JP, Altman DG, Gøtzsche PCM, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JAC, *et al*: The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928, 2011.
16. Leneva IA, Burtseva EI, Yatsyshina SB, Fedyakina IT, Kirillova ES, Selkova EP, Osipova E and Maleev VV: Virus susceptibility and clinical effectiveness of anti-influenza drugs during the 2010-2011 influenza season in Russia. Int J Infect Dis 43: 77-84, 2016.
17. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, Lu J and Xue Y: Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect 81: e21-e23, 2020.

18. Li M, Yu T, Zhu J, Wang Y, Yang Y, Zhao K, Yi Y, He J, Li C and He J: Comparison of the antiviral effect of Arbidol and Chloroquine in treating COVID-19. Ann Palliat Med 10: 3307-3312, 2021.
19. Nojomi M, Yassin Z, Keyvani H, Makiani MJ, Roham M, Laali A, Dehghan N, Navaei M and Ranjbar M: Effect of arbidol (Umifenovir) on COVID-19: A randomized controlled trial. BMC Infect Dis 20: 954, 2020.
20. Chen C, Zhang YI, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen BO, Lu M, *et al*: Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv 2020.03.17.20037432.
21. Wang ZL, Yang B, Li Q, Wen L and Zhang R: Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 71: 769-777, 2020.
22. Darazam IA, Shokouhi S, Mardani M, Pourhoseingholi MA, Rabiei MM, Hatami F, Shabani M, Moradi O, Gharehbagh FJ, Irvani SSN, *et al*: Umifenovir in hospitalized moderate to severe COVID-19 patients: A randomized clinical trial. Int Immunopharmacol 99: 107969, 2021.
23. Chen W, Yao M, Fang Z, Lv X, Deng M and Wu Z: A study on clinical effect of Arbidol combined with adjuvant therapy on COVID-19. J Med Virol 92: 2702-2708, 2020.
24. Jie X, Hongmei Y, Ping F, Kuikui Z, Bohan Y and Rui M: Beneficial effect of Arbidol in the management of COVID-19 infection. Aging (Albany NY) 13: 9253-9264, 2021.
25. Gao W, Chen S, Wang K, Chen R, Guo Q, Lu J, Wu X, He Y, Yan Q, Wang S, *et al*: Clinical features and efficacy of antiviral drug, Arbidol in 220 nonemergency COVID-19 patients from East-West-Lake Shelter Hospital in Wuhan: A retrospective case series. Virol J 17: 162, 2020.
26. Chen N, Wang X, Zhang S, Lin R and Jiang Y: Efficacy analysis of Arbidol treatment in patients with 2019 novel coronavirus pneumonia: A retrospective cohort study. Ann Palliat Med 10: 10626-10632, 2021.
27. Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, Hong Z and Xia J: Arbidol combined with LPV/r versus LPV/r alone against corona virus disease 2019: A retrospective cohort study. J Infect 81: e1-e5, 2020.
28. Xu P, Huang J, Fan Z, Huang W, Qi M, Lin X, Song W and Yi L: Arbidol/IFN-α2b therapy for patients with corona virus disease 2019: A retrospective multicenter cohort study. Microbes Infect 22: 200-205, 2020.
29. Wei S, Xu S and Pan YH: Efficacy of arbidol in COVID-19 patients: A retrospective study. World J Clin Cases 9: 7350-7357, 2021.
30. Lian N, Xie H, Lin S, Huang J, Zhao J and Lin Q: Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: A retrospective study. Clin Microbiol Infect 26: 917-921, 2020.
31. Liu MY, Wang S, Yao WF, Wu HZ, Meng SN and Wei MJ: Pharmacokinetic properties and bioequivalence of two formulations of arbidol: An open-label, single-dose, randomized-sequence, two-period crossover study in healthy Chinese male volunteers. Clin Ther 31: 784-792, 2009.
32. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, Mo X, Wang J, Wang Y, Peng P, *et al*: Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: An exploratory randomized controlled trial. Med (N Y) 1: 105-113, 2020.
33. Lan X, Shao C, Zeng X, Wu Z and Xu Y: Lopinavir-ritonavir alone or combined with arbidol in the treatment of 73 hospitalized patients with COVID-19: A pilot retrospective study. Int J Clin Pharmacol Ther 59: 378-385, 2021.
34. Chen X, Zhu B, Hong W, Zeng J, He X, Chen J, Zheng H, Qiu S, Deng Y, Chan JCN, *et al*: Associations of clinical characteristics and treatment regimens with the duration of viral RNA shedding in patients with COVID-19. Int J Infect Dis 98: 252-260, 2020.
35. Zhang JN, Wang WJ, Peng B, Peng W, Zhang YS, Wang YL, Wan Y, Chang J, Mao L, Miao XP, *et al*: Potential of arbidol for post-exposure prophylaxis of COVID-19 transmission: A preliminary report of a retrospective cohort study. Curr Med Sci 40: 480-485, 2020.
36. Yang C, Ke C, Yue D, Li W, Hu Z, Liu W, Hu S, Wang S and Liu J: Effectiveness of Arbidol for COVID-19 prevention in health professionals. Front Public Health 8: 249, 2020.
37. Jeon S, Ko M, Lee J, Choi I, Byun SY, Park S, Shum D and Kim S: Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother 64: e00819-e00820, 2020.
38. Weston S, Coleman CM, Haupt R, Logue J, Matthews K, Li Y, Reyes HM, Weiss SR and Frieman MB: Broad anti-coronavirus activity of food and drug administration-approved drugs against SARS-CoV-2 in vitro and SARS-CoV in vivo. J Virol 94: e01218-e01220, 2020.
39. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, van Bentum-Puijk W, Berry L, Bhimani Z, Bonten M, *et al*: Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 324: 1317-1329, 2020.
40. Şimşek-Yavuz S and Çelikyurt FI: An update of anti-viral treatment of COVID-19. Turk J Med Sci 51: 3372-3390, 2021.
41. Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H, Li Y, Zhao L, Li W, Sun X, *et al*: The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. Cell Discov 6: 28, 2020.
42. Boriskin YS, Leneva IA, Pécheur EI and Polyak SJ: Arbidol: A broad-spectrum antiviral compound that blocks viral fusion. Curr Med Chem 15: 997-1005, 2008.
43. Behzadi MA and Leyva-Grado VH: Overview of current therapeutics and novel candidates against influenza, respiratory syncytial virus, and middle east respiratory syndrome coronavirus infections. Front Microbiol 10: 1327, 2019.
44. Liu Q, Zhou YH and Yang ZQ: The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell Mol Immunol 13: 3-10, 2016.
45. Wang M, Wu T, Zuo Z, You Y, Yang X, Pan L, Hu Y, Luo X, Jiang L, Xia Z and Deng M: Evaluation of current medical approaches for COVID-19: A systematic review and meta-analysis. BMJ Support Palliat Care 11: 45-52, 2021.
46. Wang Y, Ding Y, Yang C, Li R, Du Q, Hao Y, Li Z, Jiang H, Zhao J, Chen Q, *et al*: Inhibition of the infectivity and inflammatory response of influenza virus by Arbidol hydrochloride in vitro and in vivo (mice and ferret). Biomed Pharmacother 91: 393-401, 2017.
47. Li H, Liu R, Zhang R, Zhang S, Wei Y, Zhang L, Zhou H and Yang C: Protective effect of arbidol against pulmonary fibrosis and sepsis in mice. Front Pharmacol 11: 607075, 2021.
48. Silin DS, Lyubomska OV, Ershov FI, Frolov VM and Kutsyna GA: Synthetic and natural immunomodulators acting as interferon inducers. Curr Pharm Des 15: 1238-1247, 2009.
49. Song Y, Zhang M, Yin L, Wang K, Zhou Y, Zhou M and Lu Y: COVID-19 treatment: Close to a cure? A rapid review of pharmacotherapies for the novel coronavirus (SARS-CoV-2). Int J Antimicrob Agents 56: 106080, 2020.
50. Pang J, Wang MX, Ang IYH, Tan SHX, Lewis RF, Chen JIP, Gutierrez RA, Gwee SXW, Chua PEY, Yang Q, *et al*: Potential rapid diagnostics, vaccine and therapeutics for 2019 novel coronavirus (2019-nCoV): A systematic review. J Clin Med 9: 623, 2020.
51. Guo YZ, Xu KJ, Li YT, Fu JD, Xu M, Yu L, Sheng JF and Zhu B: Safety of protease inhibitors and Arbidol for SARS-CoV-2 pneumonia in Zhejiang Province, China. J Zhejiang Univ Sci B 21: 948-954, 2020.
52. Jiang S, Wang R, Li L, Hong D, Ru R, Rao Y, Miao J, Chen N, Wu X, Ye Z, *et al*: Liver injury in critically Ill and non-critically Ill COVID-19 patients: A multicenter, retrospective, observational study. Front Med (Lausanne) 7: 347, 2020.