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*Article*

# Efficacy and Safety Evaluation of Arbidol in Patients with COVID-19

**Yujiao Bai[1,2], Xianqin Zhang[2], Meng Yang[1,2], Lin Zhang[3,4] and Xu Jia[1,2]**

[1] Non-coding RNA and Drug Discovery Key Laboratory of Sichuan Province, Chengdu Medical College, Chengdu, Sichuan, China
[2] School of Basic Medical Sciences, Chengdu Medical College, Chengdu, Sichuan, China
[3] College of Pharmaceutical Sciences, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China
[4] Department of Pharmacy, Shaoxing People's Hospital; Shaoxing Hospital, Zhejiang University School of Medicine, Shaoxing, Zhejiang, China
, GLOBE Institute, University of Copenhagen, Øster Farimagsgade 5, 1353, Copenhagen K, Denmark
*Corresponding author: jiaxu@cmc.edu.cn (X.J.); zhanglinfudan@zju.edu.cn (X.Z.)

**Abstract: Background** The spread of COVID-19 continues, the mutation of SARS-COV-2 is still difficult to control, and the need for antiviral drugs to treat COVID-19 remains urgent. The use of arbidol in the treatment of COVID-19 is limited and controversial. **Methods** To clarify the efficacy of arbidol on COVID-19, we collected 25 cases and 178 related studies. We analyzed the treatment information of arbidol based on the obtained cases, expanded the scope of the study, and collected current studies on the treatment of COVID-19 in various databases for in-depth analysis. **Results** History analysis showed that arbidol was effective (76% cure rate) compared with other drugs. However, compared with other antiviral drugs or standard therapy, the arbidol group had no significant advantage in reducing the time to negative virus transformation, length of hospital stays, or improvement in CT (MD=0.22, 95%CI -0.29-0.73; MD = 0.61, 95% CI 1.46 to 2.67; RR=1.15, 95%CI 0.88-1.50); Analysis of adverse events showed no significant difference between the arbidol group and the other groups (RR=0.82, 95%CI 0.25-2.71). **Conclusion** Our study showed that arbidol had no significant effect on COVID-19, but showed a slight advantage in CT improvement and adverse events. Our study objectively evaluated the efficacy of arbidol in the treatment of COVID-19 and provided some guidance for arbidol in the treatment of COVID-19.

**Highlights**

1. The COVID-19 situation is severe and the need for multiple antiviral drugs is urgent.
2. The efficacy of arbidol against SARS-COV-2 is controversial.
3. Arbidol will provide insights for the prevention and treatment of new mutant strains.
4. Arbidol had fewer adverse reactions and showed a slight advantage in CT improvement rates.
5. Arbidol alone is not recommended for the treatment of COVID-19 patients.

**Keywords:** COVID-19; SARS-Cov-2; arbidol; treatment

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection[1]. Since the outbreak of the virus in 2020, it has rapidly spread to all parts of the world, becoming a major public health event of global concern[2, 3]. The genome of SARS-COV-2 is a single - stranded positive - sense RNA, named because genome sequence detection results showed strong homology with SARS-CoV[4, 5]. Structurally, spike, membrane, nucleocapsid, and envelope proteins of SARS-COV-2 are key to drug and vaccine development[6]. Currently, some vaccines have been authorized for emergency use under WHO certification. As of November 1, according to Our World in Data of Oxford University, 7.1 billion doses of novel coronavirus vaccines have been reported globally, with a vaccination rate of 49.6%[7]. However, given the large

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population base, the increasing number of novel coronavirus variants, and the uneven epidemic prevention and control in different countries, the need for antiviral drugs remains urgent.

The effective drugs for COVID-19 need continuous attention. Molnupiravir, a small molecule drug jointly developed by Merck and Ridgeback, is expected to reduce the risk of hospitalization or death by 50% in mild-to-moderate patients[8]. Subsequently, Pfizer announced the interim results of its phase Ⅱ and Ⅲ clinical trial of Paxlovid, a small molecule novel coronavirus drug, showed that Paxlovid reduced the risk of hospitalization or death in high-risk patients by 89%[9]. On November 15, China put forward a "timetable" for COVID-19 drug research, which vividly illustrated that multiple paths were promoted simultaneously and different links "block" the virus[10]. Regrettably, the latest news announced by Merck and Ridgeback shows that Molnupiravir treatment of mild to moderate COVID-19 has an effective rate of only 30%, much lower than the 50% in the mid-term analysis[11]. The emergence of Omicron has added difficulty to COVID-19's treatment and prevention and control. Therefore, we still cannot relax vigilance for the unpredictable virus, when another round of cold winter approaches, more antiviral drugs are still needed.

Arbidol, also named umifenovir, was developed by Russian Research Center for Medicinal Chemistry and has been approved for marketing in China, Russia, and other countries[12]. Arbidol is used against influenza A and B viruses, hepatitis C virus (HCV), etc. [13]. Arbidol can inhibit the replication of SARS coronavirus and is considered a potential drug against COVID-19[14]. In the COVID-19 diagnosis and treatment protocol (trial version 8) released in China, abidol was approved for the treatment of COVID-19[15]. However, the existing clinical trials are insufficient, and there is still great controversy over whether arbidol can indeed be used as a treatment for COVID-19 or not. We analyzed collected information on the treatment of COVID-19 patients admitted from January 22 to March 5, 2020, in a hospital in Shaoxing city, Zhejiang Province, and found that arbidol appears to be beneficial to patients' recovery. To further evaluate the efficacy of arbidol in the treatment of COVID-19, we collected all relevant studies and clinical trials and discussed the application prospect of arbidol as a recommended drug for the treatment of COVID-19.

## 2. Materials and methods

### *2.1. Research object*

On the one hand, information of COVID-19 patients admitted to a hospital in Shaoxing city, Zhejiang Province from January 22 to March 5, 2020, was studied. On the other hand, studies on patients with confirmed COVID-19 diagnosis and treatment methods including arbidol were collected.

### *2.2. Data collection*

#### 2.2.1. Diagnosis and grouping of patients for history analysis

The diagnosis and typing criteria of 25 patients were based on the COVID-19 Diagnosis and Treatment Protocol (Trial Fifth Edition) issued by NHC[16]. The subjects were divided into light type, ordinary type, heavy type, and critical type. Mild and ordinary patients with mild symptoms, only fever, respiratory symptoms, imaging manifestations of pneumonia, were included in the mild symptoms group; Severe and critically ill patients with severe symptoms were included in the severe symptom group, with index oxygen saturation ≤ 93% and arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa) in resting state.

#### 2.2.2. Types of included studies and retrieval strategies

The diagnostic criteria for COVID-19 confirmed in this study refer to the COVID-19 Diagnosis and Treatment Protocol issued by the NHC (Trial version 8) [15]. Relevant research published were collected. Languages and regions were not limited. Pubmed,

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Cochrane Library, Clinical Trials, Web of Science, Embase, CBM, CNKI, Wanfang journal databases were searched by computer. All studies were published before August 24, 2021. The following search terms were used: "COVID-19", "COVID-19 Virus Disease", "SARS-COV-2", "2019-NCOV", "arbidol", "umifenovir", "RCT", etc. In addition, references included in the study were screened to avoid related studies that might be missed.

### *2.3. Data abstraction*

#### 2.3.1. Analysis of medical history

The medical history was reviewed and the diagnosis and treatment were retrospectively analyzed. All the records were summarized from the original electronic medical record and were compared by typing groups using standardized collection forms.

#### 2.3.2. Analysis of research

Data was extracted independently by two investigators and then cross-checked, any discrepancies were re-examined by a third investigator. The extracted data mainly included: first author's last name, article publication year, details of treatment strategy, sample size (N), and main outcome. According to the different treatment methods, the study was divided into the arbidol group and the control group. The control group included placebo and other antiviral drugs. Literature quality was evaluated by the Cochrane System Evaluator's Manual. Bias risk was evaluated based on the evaluation indexes, including ①Whether it was randomly assigned; ②Whether the allocation scheme is hidden; ③Blind method (for researchers and subjects as well as reviewers of the results); ④Data integrity; ⑤Other bias. Quality was assessed using the Newcastle-Ottawa Scale (NOS). NOS scores 1-3, 4-6, 7-9 were low, medium, and high, respectively[17].

### *2.4. Statistical analysis*

SPSS 25.0 software and R language (4.04) version statistical software was used for medical history analysis. Count data use case (%), tested by Fisher's exact probability method; The measurement data of normal distribution were expressed as $X \pm S$, and t-test was used for comparison between groups. The measurement data of non-normal distribution were described by a median, and the Mann-Whitney U test was used for comparison between groups. $P < 0.05$ was considered statistically significant.

Statistical software of R language (4.04) was used for effective combination and heterogeneity test. Risk ratio (RR) and mean difference (MD) were used to compare dichotomies and continuity variables, respectively. We use both the fixed effect model and random effect model to prevent heterogeneity from affecting the reliability of the results. All results were presented with 95% CI. Heterogeneity was assessed using the statistic I2 value. Visualization analysis through forest plots is a common method. However, forest plots only showed results with fixed significance thresholds at $P < 0.05$[18]. Drapery plots were also generated to visualize how the results varied with different significance thresholds. According to the recommendation of the Cochrane Manual[19], the study only used a funnel plot to make a brief judgment on publication bias, because there were less than 10 studies included for each outcome indicator.

## 3. Results

Our study retrospectively analyzed 25 cases from Shaoxing Hospital and 178 related studies collected from various databases. The effectiveness of arbidol in the treatment of COVID-19 was objectively evaluated based on the actual treatment situation of hospitals and the results of big data analysis.

### *3.1. Analysis of medical history*

#### 3.1.1. General information of patients

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In the retrospective analysis of medical history, 16 patients (64%) in the mild group and there was no significant difference in age between severe and mild groups (P > 0.05, Table 1). Among the 25 patients, 13 patients had a history of chronic diseases, and there was statistical significance in whether there were chronic diseases between the two groups (P < 0.05, Table 1). The above results suggested that the middle-aged and the elderly are the main patients, and there was no high correlation between age and severity of the disease. However chronic disease was a risk factor for the severity of the disease.

**Table 1.** General characteristics of patients with different clinical types.

| Normal information | Mild group | | Severe group | | Total (n=25) |
|---|---|---|---|---|---|
| | Light (n=3) | Common (n=13) | Severe (n=6) | Critical (n=3) | |
| Sex | | | | | |
| Male | 1 (33.33%) | 6 (46.15%) | 4 (66.67%) | 3 (100.00%) | 14 (56.00%) |
| Female | 2 (66.67%) | 7 (53.85%) | 2 (33.33%) | 0 (0.00) | 11 (44.00%) |
| Age | | | | | |
| x ± s, years | 32.00±5.57 | 51.23±13.40 | 50.67±9.27 | 58.33±23.76 | 49.64±14.40 |
| < 45 | 3 (100.0%) | 4 (30.77%) | 1 (16.67%) | 1 (33.33%) | 9 (36.00%) |
| 45 ~ 60 | 0 (0.00) | 5 (38.46%) | 4 (66.67%) | 0 (0.00) | 9 (36.00%) |
| > 60 | 0 (0.00) | 4 (30.77%) | 1 (16.67%) | 2 (66.67%) | 7 (28.00%) |
| Chronic disease | | | | | |
| Have | 1 (33.33%) | 4 (30.77%) | 4 (66.67%) | 3 (100.00%) | 12 (48.00%)* |
| No | 2 (66.67%) | 9 (69.23%) | 2 (33.33%) | 0 (0.00) | 13 (52.00%) |

Note: *, P＜0.05, compared to the mild group, the severe group had a significant difference.

3.1.2. Treatment of patients

All 25 patients received antiviral drugs, 14 patients (56%) combined with hormone therapy, and 21 patients (84%) were cured and discharged from the hospital. Of the 21 discharged patients, 76% were treated with arbidol. Two patients were treated only with arbidol, and all of them were cured and discharged. Twenty-three patients were treated with arbidol and lopinavir in combination, and 19 (82.6%) were cured and discharged from the hospital (Table 2). In the group of antiviral drugs plus hormone therapy, 14 patients were treated with arbidol + lopinavir + methylprednisolone sodium succinate, with a discharge rate of 71% (Table 2). There was no significant difference in the time of virus turning negative between the mild and severe symptom groups (P =0.07 > 0.05, Figure 1). However, there was a significant difference between the arbidol group and the arbidol combine hormone group (P =0.026< 0.05, Figure 2).

**Table 2.** Treatment of 25 patients with COVID-19.

| Treatment | Count | Cured number |
|---|---|---|
| Arbidol | 2 (8%) | 2 (2A) |
| Arbidol+ Lopinavir | 9 (36%) | 9 (9A) |
| Arbidol+ Lopinavir+Methylprednisolone sodium succinate | 14 (56%) | 10 (5A,5B) |

Note: A: Arbidol group; B: Arbidol in combination with methylprednisolone sodium succinate group.

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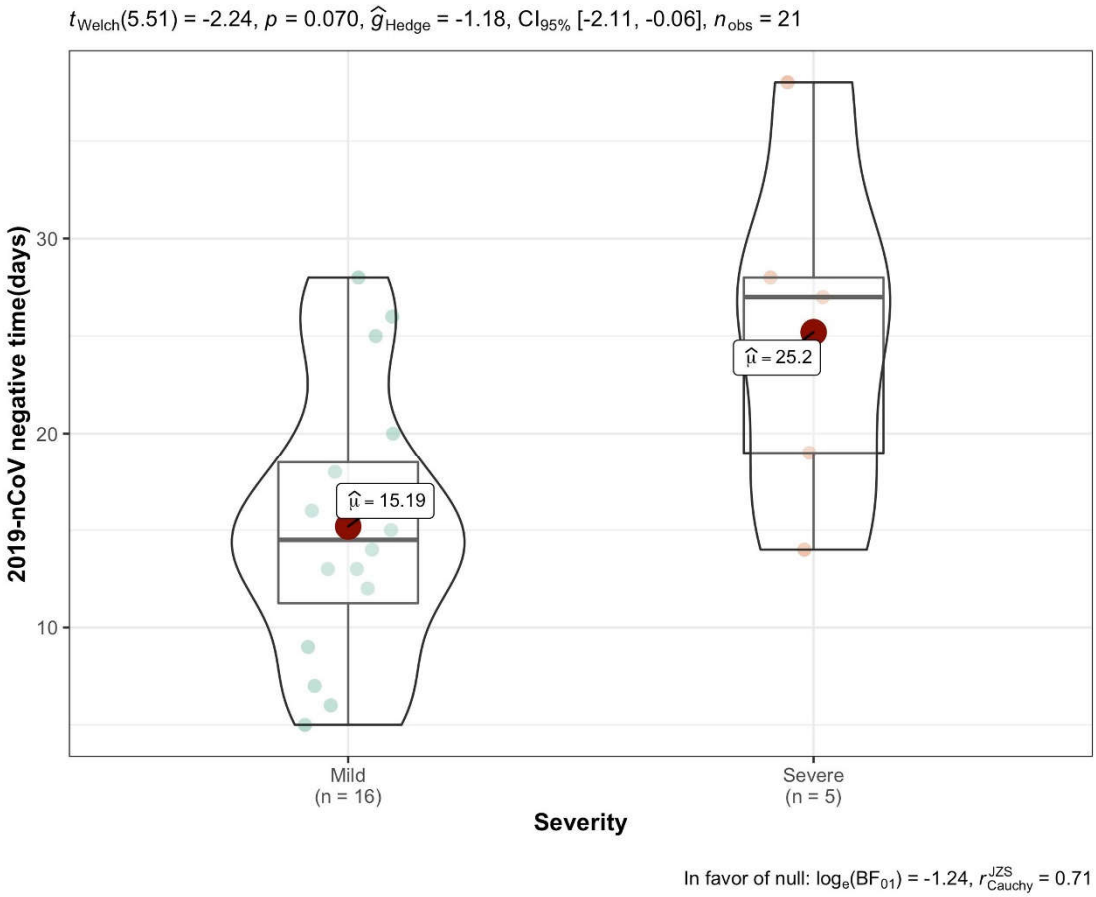


**Figure 1.** Comparison of COVID-19 negative time between mild and severe patients.

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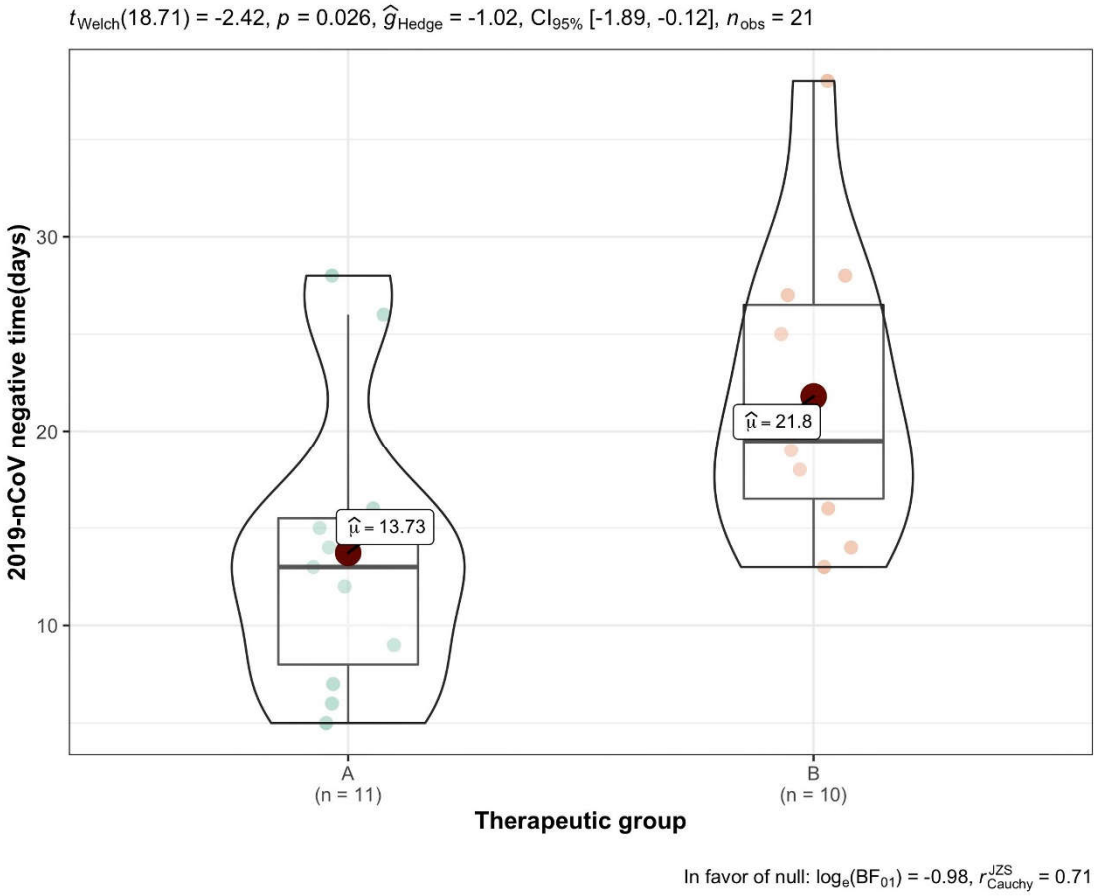


**Figure 2.** Comparison of COVID-19 negative time among different therapeutic options.
Note: A: Arbidol, B: Arbidol+Methylprednisolone Sodium Succinate.

In short, the above case analysis results suggested that arbidol may be effective in the treatment of COVID-19, while the combination therapy of methylprednisolone sodium succinate and arbidol was not effective in shortening the time to negative virus transformation.

*3.2. Analysis of research*

A total of 178 pieces of related studies were retrieved, and 11 studies were finally included for further analysis after the screening and selection process of qualifying trials[20-30]. The search process was shown in Figure 3.

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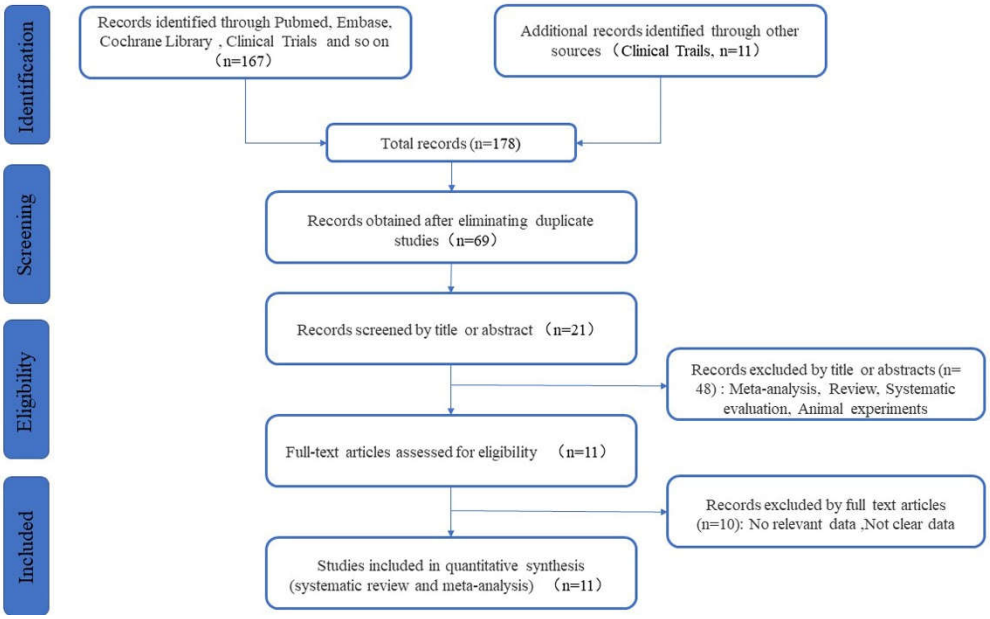


**Figure 3.** PRISMA diagram of study selection.

3.2.1. Analysis of the time of virus turning negative

Six studies were included in the analysis of time to negative virus conversion[22, 23, 25, 26, 28, 30]. After heterogeneity test, $I^2$=25%, and P=0.25 > 0.1, suggesting low heterogeneity among literatures in this study (Figure 4A). The funnel plot results correspond to these results (Figure 4B). The fixed-effect model combined the results of all studies, resulting in an MD=0.22 with a 95%CI of －0.29 - 0.73, suggesting that there was no significant difference between arbidol and other antiviral drugs or placebo in shortening the time to negative virus transformation. Drapery plots results showed the same overall trend as forest plots (Figure 4C). The shaded area represented the prediction interval, which was wider than the confidence interval of the combined effect of the forest plot. But there was no statistically significant difference between arbidol and other groups in the time of virus turning negative.

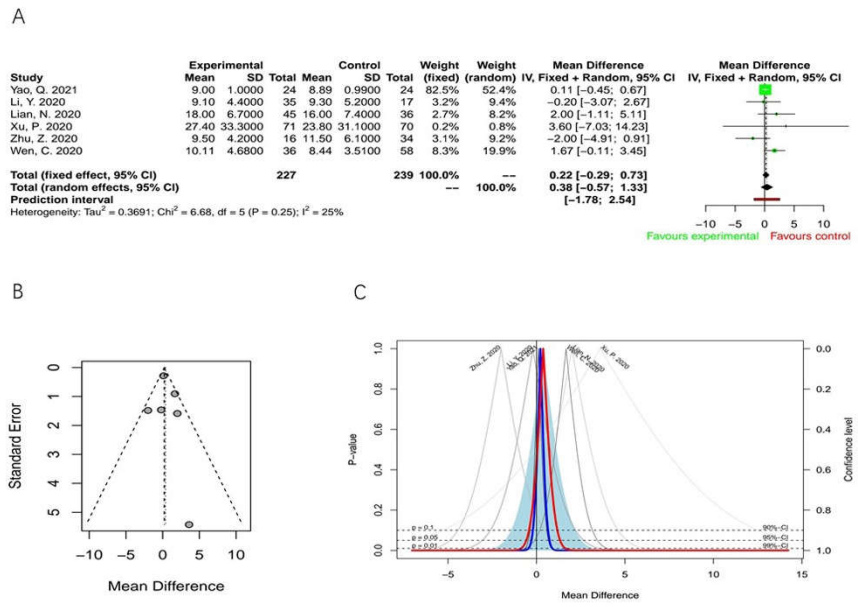


**Figure 4.** Analysis of the time of virus turning negative.

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Note: A: Forest plots showed a forest map of time to negative virus transformation compared to other antiviral drugs or placebo. B: Funnel plots for evaluating the publication bias of the included literature on the time of virus turning negative. C: Drapery plots for virus turning negative, and redline represents random-effects model, blueline represents fixed effect model, shaded area represents range of prediction.

### 3.2.2. Analysis of hospital stays

Five studies were included in the length of hospital stay analysis[20, 23, 24, 26, 27]. There was heterogeneity among the literature selected for this study ($I^2$=73%, and P < 0.01) (Figure 5A). Further investigation of the funnel plot suggested that there was a strong possibility of heterogeneity in one of the literatures. In this case, two effect model results were consistent (fixed effect model: MD=0.84, 95%CI-0.10-1.78; Randomized effect model: MD=0.61,95%CI -1.46-2.67), suggesting that patients receiving arbidol had little benefit in terms of length of hospital stay compared with other antiviral drugs or placebo. Drapery Plots analysis showed the same results (Figure 5C).

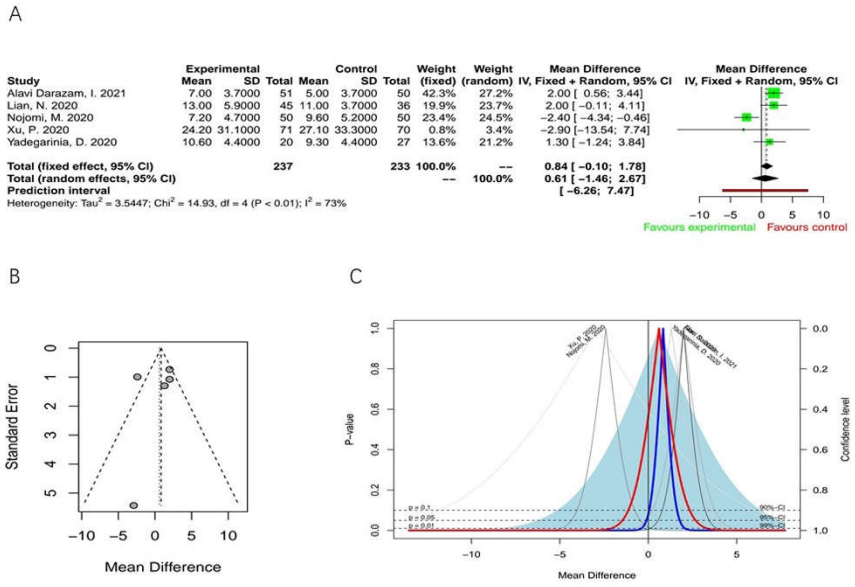


**Figure 5.** Analysis of hospital stays.

Note: A: Forest plots showed a forest plot of length of stay analysis compared to other antiviral drugs or placebo. B: Funnel plots for evaluating publication bias in the included literature on length of stay. C: Drapery plots for the length of stay, and redline represents random-effects model, blueline represents fixed effect model, shaded area represents range of prediction.

### 3.2.3. Analysis of CT improvement rate

Six studies included CT improvement rate analysis[21, 22, 24, 25, 28, 29]. And they were heterogeneity ($I^2$=69% and P < 0.01) (Figure 6A). Funnel plot results suggested that it might be related to the heterogeneity of two kinds of literature (Figure 6B). The random-effect model was selected, and the total RR was 1.15 (95%CI 0.88-1.50) (Figure 6A). The predicted range of Drapery plots showed that the difference between the arbidol group and the control group was not strong, but it was generally biased towards the control group (Figure 6C). In summary, arbidol had an advantage in improving lung CT, but the degree of improvement was not statistically significant, that is, there was no significant difference in CT improvement between arbidol and other antiviral drugs or placebo from a statistical perspective.

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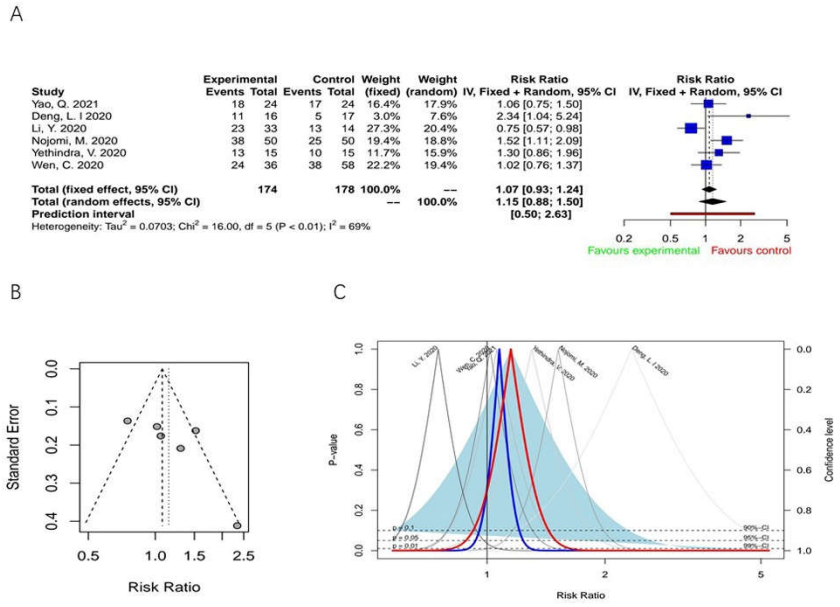


**Figure 6.** Analysis of CT improvement rate.

Note: A: Forest plots showed CT improvement rate analysis compared to other antiviral drugs or placebo. B: Funnel plots were evaluated for inclusion bias in the literature regarding CT improvement rates. C: Drapery plots for CT improvement rates, and redline represents random-effects model, blueline represents fixed effect model, shaded area represents range of prediction.

### 3.2.4. Analysis of adverse reaction

Adverse reaction analyses were included in five studies[22-25, 28]. As shown in figure 7, the results of the two effect models were consistent (fixed effect model: RR=0.77, 95%CI 0.44-1.34; Random effect model: RR=0.82, 95%CI 0.25-2.71). Trends in the total RR values and the range predicted by drapery plots indicated that arbidol reduced adverse events compared with other antiviral drugs or placebo, but the magnitude of the reduction did not show statistical significance (Figure 7).

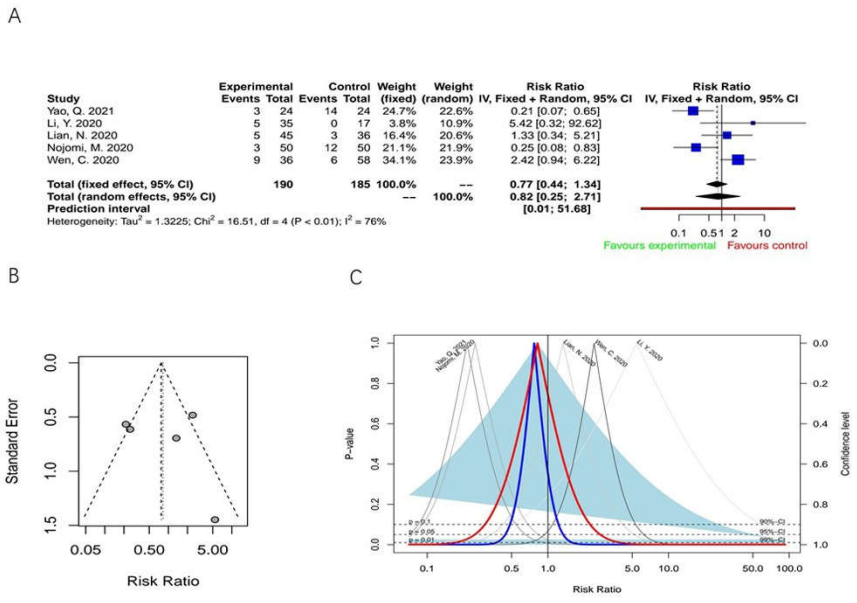


**Figure 7.** Analysis of adverse reaction.

Note: A: Forest plots showed a forest plot of adverse reactions analyzed compared to other antiviral agents or placebo. B: Funnel plots were evaluated for publication bias in the included literature on

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adverse reactions. C: Drapery plots for adverse reactions, and redline represents random-effects model, blueline represents fixed effect model, shaded area represents range of prediction.

In summary, the results of the above analysis suggested that arbidol has no significant effect on reducing the time to negative nucleic acid conversion, length of hospital stay, or improvement in CT, which means taking arbidol has no significant benefit for the treatment of COVID-19. However, the improvement of CT showed a good trend, and no adverse events caused concern when taking arbidol.

## 4. Discussion

The results of our case study indicate that the majority of COVID-19 patients are middle-aged and elderly, and the combination of chronic underlying diseases is a risk factor for the severity of COVID-19. Among the 25 patients, 12 patients (48%) had underlying diseases such as hypertension, diabetes, and chronic liver disease, and the proportion of severe symptoms combined with underlying diseases was significantly higher than that of the mild symptoms group, indicating that patients with underlying diseases are high-risk groups for developing severe and critical COVID-19 patients. This result is consistent with the research results of others[31, 32]. The reason that chronic underlying diseases are high-risk factors was analyzed, which is related to the pathogenesis of SARS-COV-2 [33]. For COVID-19 patients with chronic underlying diseases, priority care should be given to their clinical treatment and timely symptomatic treatment measures should be taken.

The treatment of 25 patients in our study suggests the efficacy of arbidol in the treatment of COVID-19. Two patients in the mild symptom group were treated with arbidol only as an antiviral drug without hormone use or non-invasive ventilation and were successfully cured. Although self-limiting conditions do exist, it is difficult to rule out the role of arbidol. 23 patients were treated with arbidol combined with lopinavir, and the cure rate was 82.6%. Although 9 patients were treated with arbidol combined with lopinavir, studies have shown that lopinavir is ineffective in the treatment of COVID-19[34, 35], and in the randomized trial of Cao B et al. [35], the results clearly showed that for severe COVID-19 patients, Treatment with lopinavir/ritonavir did not reduce mortality or sarS-COV-2 virus conversion time. It was consistent with the results of Naveen V. [36] and Chunguang Yang et al. [37], which reflected the potential therapeutic effect of arbidol from aside.

Further studies are needed to determine whether arbidol should be used in combination with the hormone methylprednisolone sodium succinate to treat COVID-19. Compared with methylprednisolone sodium succinate, uncombined treatment was more beneficial to reduce the detectable duration of viral RNA. On the one hand, the therapeutic effect of methylprednisolone sodium succinate is not strong, and other treatment methods should be adopted for severe patients. On the other hand, patients in our study began to use methylprednisolone sodium succinate at the later stage of treatment, which may be related to the time of methylprednisolone sodium succinate medication. Current recommendations for the use of corticosteroids for COVID-19 remain mixed[38]. Therefore, more clinical trials are needed to provide evidence of methylprednisolone succinate as a treatment for COVID-19.

The results of the big data study on the use of arbidol in the treatment of COVID-19 found that the addition of arbidol showed no significant advantage in shortening the time to negative virus transformation, length of hospital stay, or improvement in CT. However, the results of all three studies showed that arbidol was effective in shortening the time of virus turning negative, the length of hospital stay, and the improvement of CT. The reason for the insignificant antiviral effect of arbidol remains unclear. In the studies of Nojomi M., Yethindra V., Yadegarinia, D. et al.[24, 27, 29], arbidol showed significant efficacy. The reason for the difference may be related to the setting of group control. Our studies involved arbidol versus lopinavir/ritonavir, IFN-$\alpha$2b, and arbidol versus placebo or standard therapy. This difference in drug combinations may be a confounding factor in the results. Differences in the severity of the patient's illness across studies may be another

point of confusion. The difference in efficacy of arbidol between mild and severe groups is unclear, and more research is needed to determine whether arbidol can be more effective in treating COVID-19 at certain stages of the disease.

Arbidol has no significant side effects in the treatment of COVID-19, but the low number of adverse reactions may be its advantage. In several studies[22-25, 28] that we included in the analysis of the adverse reaction, the incidence of adverse events of arbidol was about 80% compared with other antiviral drugs or standard treatment groups, and the main adverse reactions were diarrhea and nausea. The success of Qianshadong and Pfizer's research on specific drugs for COVID-19 is no doubt surprising. However, neither study has been fully tested in clinical trials, and we need to pay more attention to whether there are safety issues with its use around the world.

Our study has limitations. First of all, due to the small number of case data and difficulty in the grouping, case studies were not included in the subsequent research analysis. The results of case studies are only taken as a starting point, and more scientific research data methods are used to make up for the shortcomings of fewer cases. In addition, in research studies, differences in grouping and duration of medication among study results may be another limitation, which is related to the unknown efficacy of arbidol in patients with different conditions. Finally, our study did not consider the possibility of the emergence of SARS-COV-2 variants. Whether different SARS-COV-2 variants reduce the drug sensitivity of arbidol remains unknown.

## 5. Conclusion

In conclusion, we found that treatment with arbidol did not significantly reduce the time to viral conversion, length of hospital stays, or improve lung CT, but it had an advantage in improving lung CT and adverse events. We expect these early data to inform future studies that will play a role in evaluating the efficacy of arbidol against SARS-COV-2 infection. Whether arbidol in combination with other antiviral agents may enhance antiviral effects and improve clinical outcomes remains to be determined.

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**Ethical Approval statement:** These studies complied with all applicable regulations.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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