Arbidol against COVID-19: A Comprehensive Systematic Review and Meta-Analysis

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Abstract

Objective: To provide the latest evidence on the efficacy and safety of Arbidol (Umifenovir) in COVID-19. Methods: A comprehensive systematic search of the evidence was carried out in PubMed, Cochran library, Embase, and Medrxiv up to October 1, 2020. The Cochrane risk of bias tool and Newcastle-Ottawa Scale checklist were used for assessing the quality of studies. Meta-analysis was performed using RevMan (version 5.3). Results: Fifteen studies were met for the inclusion. No significant difference was observed between Arbidol and control groups in terms of primary outcomes, including negative rate of PCR (NR-PCR) on 7 days (risk ratio [RR] 0.89; P=0.37) and 14 days (RR: 1.10;P=0.17), negative conversion time (NCT) (mean difference [MD]: 0.74; P=0.37), and as well as secondary outcomes (P<0.05). Compared with LPV/r, Arbidol showed a better efficacy in terms of NR-PCR on 14 days (P=0.02). In contrast, NCT in LPV/r was higher (P=0.007). However, not significant difference was found in terms of NR-PCR on 7 days (P=0.05). Adding Arbidol to LPV/r was led to a better efficacy in terms of NR-PCR on 7 days and NCT (P<0.05). Nevertheless, it was not significant reading NR-PCR on 14 days (P=0.99). There is no significant difference Arbidol vs. Interferon /Arbidol and IFN/Arbidol vs. Interferon (P<0.05). Conclusion: Arbidol was not superior to control against COVID-19. Additionally, not major treatment effect was found compared with other therapeutic agents. There are needed well-designed studies with large sample size to establish on efficacy and safety of Arbidol.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causing agent of coronavirus disease 2019 (COVID-19), has rapidly spread throughout the world, leading to a pandemic (1-3). Despite the lack of approved treatment for COVID-19 (4), some antiviral drugs have been proposed as promising therapeutic options against SARS-CoV-2 infection, including Interferon (5, 6), Lopinavir/ritonavir (7), Chloroquine (8), Remdesivir(9), and Arbidol (10).

Arbidol is an oral antiviral drug (11) approved in Russia and China decades ago for prophylaxis and treatment of influenza groups A and B and other respiratory viral infections(12). Umifenovir is the generic name for Arbidol. Various studies have shown its antiviral and anti-inflammatory activity for different types of influenza viruses (13-17), especially influenza A virus subtype H1N1 (A/H1N1) (14). Its broad-spectrum antiviral activity against other viruses, such as Zika Virus (18), Ebola virus (19), Hepatitis B and C virus (19-22), Rhinovirus (23), respiratory syncytial virus (23, 24), Coxsackie virus (23, 25), Chikungunya virus(26), and Adenovirus (23) is shown in vitro and in vivo.

Several in vitro studies (27, 28) have evaluated Arbidol's potential therapeutic effects on SARS-CoV-2 infection. A study indicated the efficacy of Arbidol against SARS-CoV-2 by blocking trimerization of the spike glycoprotein (27). In another study, Wang and et al. examined the antiviral activities of recommended anti-influenza drugs by WHO, including Baloxavir, Laninamivir, Oseltamivir, Peramivir, Zanamivir, and Arbidol against SARS-CoV-2. The result of this study showed that only Arbidol, compared with the other five drugs, efficiently inhibited SARS-CoV-2 infection (28).

The evidence on the anti-virus effect of Arbidol against SARS-CoV-2 is controversial. Some studies suggested its beneficial effects either as monotherapy or in combination with other agents for COVID-19 (7, 29-31), while others studies have found no benefit for using Arbidol for COVID-19 patients (32, 33). Therefore, there is an urgent need to reach a conclusive decision on its usage for COVID-19. We have conducted this comprehensive systematic review and meta-analysis to provide the latest evidence on Arbidol's efficacy and safety compared with other treatments in COVID-19.

Methods

We have registered the protocol of this systematic review and meta-analysis with the registry number of CRD42020207821. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist when writing this report.

Literature search strategy

We conducted a systematic search in the leading bibliographic, including PubMed, The Cochran Library, Embase, Scopus, and Web of Science for the relevant records up to October 1, 2020. We searched Medrxiv, Google Scholar, and clinical registry databases, including Clinical trial Gov, the European Union Clinical Trials Register, and the Chinese Clinical Trial Registry for additional relevant documents. Finally, we scanned the references list of the included studies and review articles. There was no restriction on the language. Search terms included 2019-nCoV, SARS-CoV-2, COVID-19, Arbidol, and Umifenovir.

Study selection

Two authors independently screened identified records based on inclusion and exclusion criteria. Disagreements between those authors were resolved by discussion among authors. The studies were included based on the following criteria: (1) Patients with laboratory-confirmed COVID-19; (2) Arbidol as monotherapy or in combination with other pharmaceutical therapeutic agents; (3) Any therapeutic interventions and or placebo as a comparison (4); clinical improvement and mortality rate as outcomes; (5) clinical trials or observational studies. The exclusion criteria were the studies conducted on animal models, case reports, letters to editors, and editorial.

Data Extraction and Quality Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias to assess the quality of randomized clinical trials. We conducted quality assessment of observational studies using the Newcastle Ottawa Scale.

We extracted data using the same data extraction form. The extracted data was including (1) Study Characteristics (author, year, setting, and design); (2) patient's characteristics (sample size, sex, and age); (3) Intervention and comparison (sample size and dose); (4) efficacy and safety outcomes. All the above steps were performed independently by two authors.

Evidence synthesis

We performed meta-analysis using RevMan software, version 5.3. Mean difference (MD) with a 95% CI was used for continuous variables. We used risk ratio (RR) with a 95% confidence interval (CI) for dichotomous variables. We evaluated statistical heterogeneity using the I^2 and chi-square tests. We used the random-effects method for studies with I^2>50% and or Chi-square with a significance level $p < 0.1$. Otherwise, we used the fixed-effect method. We summarized the evidence for the studies which could not be meta-analyzed due to a lack of common variables.

Results

Studies characteristics

Figure 1 shows the literature search flow, removal of duplicates, and screening based on title, abstract, and full text. Finally, we reviewed 33 full-text articles. We included two randomized clinical trials and 13

retrospective studies in the final analysis. The characteristics of the studies included in the systematic review are presented in table 1.

[Figure 1 goes here]

[Table 1 goes here]

Outcomes

Arbidol vs. Control

The result of meta-analysis showed that there was no significant difference between Arbidol and control groups in terms of negative rate of PCR on 7 days (RR: 0.89; 95% CI: 0.69 to 1.15; P=0.37) and on 14 days (RR: 1.10; 95% CI: 0.96 to 1.25; P=0.17), rate of improvement at chest CT on 7 days (RR: 1.53; 95% CI: 0.50 to 4.68; P=0.46) and on 14 days (RR: 0.92; 95% CI: 0.56 to 1.54; P=0.76), rate of cough alleviation on 7 days (RR: 1.47; 95% CI: 0.64 to 3.39; P=0.36) and on 14 days (RR: 1.19; 95% CI: 0.74 to 1.91; P=0.47), hospital stay (MD: 3.97; 95% CI: 0.05 to 7.89; P=0.05), disease progression (RR: 1.69; 95% CI: 0.40 to 7.17; P=0.48), and negative conversion time (MD: 0.74; 95% CI: -0.87 to 2.34; P=0.37) (Fig 2). Arbidol was associated with higher adverse events compared with control (RR: 2.24; 95% CI: 1.06 to 4.37; P=0.04) (Fig 3).

Arbidol vs. Other therapeutic agents

Arbidol vs. Favipiravir

Only one study (34) compared Arbidol (200mg*3/day for 10 days) with Favipiravir (1600mg*2/first day followed by 600mg*2/day for 10 days). The result showed no significant difference between Arbidol and Favipiravir groups for the clinical recovery rate (51.67% vs. 61.21%, P=0.1396). Compared with Arbidol, Favipiravir was associated with better efficacy in relieving pyrexia and cough (P<0.0001). The frequency of drug-related adverse events for Arbidol and Favipiravir were 23.33% and 31.9%, respectively (P= 0.1410).

Arbidol vs. Chloroquine

The result of the meta-analysis showed that there is no significant difference between Arbidol and Chloroquine in terms of the negative rate of PCR (RR: 1.10; 95% CI: 0.86 to 1.42; P=0.46) and negative conversion time (MD: 0.69; 95% CI: -3.72 to 5.10; P=0.76) (Table 2). In contrast, the length of hospital stay in patients taking Chloroquine was significantly shorter than patients taking Arbidol (MD: 4.59; 95% CI: 0.59 to 8.60; P=0.02) (Table 2).

Arbidol vs. Oseltamivir

Xudan Chen et al. (32) found that the clearance rate 14 days for Arbidol and Oseltamivir were 75.7% and 61.5%, respectively. The median length of hospital stay in both groups was similar (23 days). The result of another study (30) showed that Arbidol was superior to Oseltamivir in reducing mortality. The adjusted OR for Arbidol and Oseltamivir was 0.183 (95% CI, 0.075 to 0.446; P<0.001) and 0.220 (95% CI, 0.069 to 0.707; P=0.011), respectively. Also, Arbidol was better for the reduction in lesion size (46.43% vs. 41.18%).

Arbidol vs. LPV/r

Arbidol showed better efficacy compared LPV/r in terms of negative rate of PCR on 14 days (RR: 1.47; 95% CI: 1.06 to 2.04; P=0.02). However, the negative conversion time in LPV/r was higher (MD: -2.28; 95% CI: -3.83 to - 0.72; P=0.004) (Table 2). Nevertheless, there was no significant between two drugs in terms of negative rate of PCR on 7 days (RR: 1.54; 95% CI: 1.00 to 2.37; P=0.05), rate of improvement at chest CT on 7 days (RR: 1.14; 95% CI: 0.77 to 1.69; P=0.05) and 14 days (RR: 0.99; 95% CI: 0.80 to 1.23; P=0.92), rate of cough alleviation on 7 days (RR: 1.61; 95% CI: 0.21 to 12.22; P=0.64) and 14 days (RR: 0.81; 95% CI: 0.58 to 1.15; P=0.24), hospital stay (MD: -1.83; 95% CI: -13.59 to 9.92; P=0.76), disease progression (RR: 1.08; 95% CI: 0.13 to 9.29; P=0.94) (Table 2). Compared with LPV/r, Arbidol had lower adverse events (RR: 0.49; 95% CI: 0.30 to 0.81; P=0.006) (Table 2).

Arbidol plus LPV/r vs. LPV/r

The result showed that Arbidol combined with LPV/r vs. LPV/r alone was associated with a significant difference in terms of the negative rate of PCR on 7 days (RR: 2.06; 95% CI: 1.13 to 3.76; P=0.02) and negative conversion time (MD: 3.49; 95% CI: 1.99 to 4.99; P<0.05) (Table 2). However, not significant effect was observed between two treatments in terms of negative rate of PCR on 14 days (RR: 0.99; 95% CI: 0.55 to 1.80; P=0.99), rate of improvement at chest CT on7 days (RR: 1.05; 95% CI: 0.20 to 5.50; P=0.96), and hospital stay (MD: -2.62; 95% CI: -4.52 to - 0.71; P=0.007) (Table 2).

Arbidol and IFN

The meta-analysis result showed no significant difference between Arbidol alone and IFN/Arbidol Combination regarding the negative conversion time (MD: -0.99; 95% CI: -16.67 to 14.69) (Table 2). Also, IFN/Arbidol Combination did not show benefit compared with Interferon alone regarding negative conversion time (MD: 2.37; 95% CI: -7.78 to 12.40) (Table 2). Yaya Zhou et al. (35) found that the length of stay in hospital for patients taking IFN/Arbidol Combination was shorter Arbidol alone (26 days vs. 18 days; P <0.001). In another study (36), there was no significant difference between patients taking IFN/Arbidol and patients taking Interferon in terms of hospitalization and RNA clearance days. However, the absorption of pneumonia in the combined group was faster.

Discussion

The aim of this study was to examine the available evidence on the efficacy and safety of Arbidol in the treatment of COVID-19 patients. The finding of the meta-analysis showed that Arbidol was no superior in controlling all primary and secondary outcomes, including the negative rate of PCR, negative conversion time, rate of improvement at chest CT, cough alleviation, hospital stay, and disease progression.

Similar to our finding, a meta-analysis by Huang et al. (37) indicated that Arbidol was not associated with significant improvement in terms of efficacy outcomes, including negative conversion time, a negative rate of PCR on day 7, rate of alleviation in cough and fever, and hospital stay. However, they found that Arbidol was better than control regarding the negative rate of PCR on day 14, which contrasts with our findings. In another meta-analysis done by Li et al. (38), Arbidol was associated with a significant improvement compared with control for negative rate of PCR in patients with COVID-19. Nevertheless, those found no efficacy for negative conversion time and improvement rate at chest CT and disease.

Differences in control groups contributed to this conflicting finding between meta-analyses. In our study, we used more specific criteria on treatments in control groups due to undertaking a comprehensive systematic review and meta-analysis. Our control groups included no antiviral treatment, while in Huang et al.'s study, the comparison group was no Arbidol treatment and in another study were other antiviral drugs or without any antiviral drug. It should be noted that the use of different types of control groups in meta-analysis can have problems including risk of bias, heterogeneity, imprecision, and finally affect the interpretation of findings(39).

Although the present study found no treatment benefit for Arbidol, recent findings from two studies (40, 41) have suggested its efficacy and safety as prophylaxis treatment in patients with COVID-19. The result from a Clinical and laboratory data analysis (40) showed that Arbidol led to reducing SARS-CoV-2 infection while does not affect the hospitalization rate. Zhang et al. (41) found that Arbidol was associated with a reduction in SARS-CoV-2 infection. It seems that more evidence is needed to conclude regarding the potential of Arbidol for prophylaxis of COVID-19.

The finding of the meta-analysis of Arbidol vs. other therapeutic options was different. Arbidol was not more effective than Chloroquine in efficacy outcomes, and Chloroquine was better regarding the length of hospital stay. However, patients taking Arbidol showed better efficacy than Oseltamivir for the clearance rate of 14 days, the median length of hospital stay, and mortality rate.

Compared with LPV/r, Arbidol was associated with a higher negative PCR rate on 14 days. In contrast,

the negative conversion time in LPV/r was higher. However, both were similar in terms of negative rate of PCR on 7 days, rate of improvement at chest CT, cough alleviation, hospital stay, and disease progression.

Several study evaluated the potential treatment effect of Arbidol in combination with LPV/r on COVID-19 patients. Our meta-analysis showed that adding Arbidol to LPV/r increased the negative rate of PCR on 7 days and negative conversion time compared to LPV/r alone. However, Arbidol has no treatment effect for other efficacy outcomes, including negative rate of PCR on 14 days, rate of improvement at chest CT and hospital stay. This meta-analysis showed that Arbidol added to Interferon did not increase the negative conversion time in patients. Similar results were also found for adding Interferon to Arbidol. However, a retrospective cohort study (35) found that the median length of hospital stay in combination therapy with IFN/Arbidol was shorter than control.

Although Arbidol was associated with higher adverse events in patients, no serious adverse events were observed. Some patients experienced diarrhea, nausea, and loss of appetite.

Limitations

There were several significant limitations to the current study. One of the challenging limitations of our study was the setting of the study. All studies were conducted in China, which prone our finding to selection bias, which is a threat to the validity of our meta-analysis. To solve this issue, it can be useful the strategies recommended by Almeida et al. (42) for reducing bias. Another limitation was the study design. Studies included in our meta-analysis were retrospective and were associated with higher bias and confounders. It should be noted that in lack of RCT, the finding of a meta-analysis of observational studies can be reliable.

Finally, we could not perform subgroup analysis based on treatment duration, drug dose, and other variables due to a small number of studies.

Conclusion

The finding of this meta-analysis revealed that Arbidol was no superior to control in patients with COVID-19. Additionally, no significant treatment effect was observed compared with other therapeutic agents. Well-designed randomized controlled trials with large sample size are necessary to conclude the efficacy and safety of Arbidol against COVID-19.

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None

Conflict of interest

The authors declare that there is no conflict of interest.

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Table 1 Characteristics of included studies

Study	Country	Design	N (M:F)	Intervention (n)	Comparison (n)
Chang Chen	China	RCT	236 (110:126)	Arbidol	Favipiravir
Hui Huang	China	R	27 (12:15)	Arbidol	LPV/r, CQ
Lanjuan Li	China	R	111 (47:64)	Arbidol+ER	ER
Lisi Deng	China	R	33(17:16)	Arbidol + LPV/r	LPV/r
N. Lian	China	R	81(45:56)	Arbidol	Control (without Arbidol)
Ping Xu	China	R	141(74:67)	Arbidol+IFN (71)	IFN (70)
Qibin Liu	China	R	504	Arbidol	Os, LPV/r
Qiong Zhou	China	R	77 (31:46)	Arbidol (24)	Arbidol+IFN(46), IFN(7)
Wenyu Chen	China	RCT	62(34:28)	Arbidol+ Control	Control
Xiu lan	China	R	73 (37:36)	Arbidol + LPV/r	LPV/r
Xudan Chen	China	R	284 (131:153)	Arbidol (60)	Control (121), LPV/r(60), Arbidol + LPV/r (16),
Yaya Zhou	China	R	221 (95: 126)	Arbidol (82)	Arbidol+IFN (139)
Yueping Li	China	RCT	44 (23:21)	Arbidol (16)	LPV/r (21), Control (7)
Zhen Zhu	China	R	50 (26:24)	Arbidol (16)	LPV/r (34)
C Y Wen	China	R	178	Arbidol	LPV/r (21), Control (7),), Arbidol + LPV/r (16)

R: Retrospective; RCT: Randomized Clinical Trial; CQ: Chloroquine; IFN: Interferon; LPV/r: Lopinavir/Ritonavir; ER: The empirical regimens included Interferon-α, LPV/R, Favipiravir, Ribavirin, Darunavir/Cobicistat; Os: Oseltamivir

Table 2 Pooled estimate of Arbidol vs. other therapeutic agents

Analysis	No. of studies	Sample size	Pooled estimate (%95CI)	P	Heterogeneity
					Ch^2
Arbidol vs. CQ					
Negative rate of PCR on 14 days	2	75	1.15 [0.88, 1.49]	0.31	0.07
Negative conversion time	2	75	0.69 [-3.72, 5.10]	0.76	14.71
Hospital stay	2	75	4.59 [0.58, 8.60]	0.02	8.44
Arbidol vs. LPV/r					
Negative rate of PCR on 7 days	3	214	1.54 [1.00, 2.37]		2.57
Negative rate of PCR on 14 days	5	238	1.47 [1.06, 2.04]	0.02	24.07
Negative conversion time	5	328	-2.28 [-3.83, -0.72]	0.004	21.91
Hospital stay	2	114	-1.83 [-13.59, 9.92]	0.76	29.42
Imrovement at CT on 7 days	2	156	1.14 [0.77, 1.69]	0.67	0.29
Imrovement at CT on 14 days	2	156	0.99 [0.80, 1.23]	0.92	0.24
Disease progress	2	164	1.08 [0.13, 9.29]	0.94	5.64
Imrovement at Cough on 7 days	2	141	1.61 [0.21, 12.22]	0.64	5.48
Imrovement at Cough on 14 days	2	141	0.81 [0.58, 1.15]	0.24	0.32
Time to recovery	2	144	1.04 [0.82, 1.32]	0.78	0.25
Adverse events	3	181	0.49 [0.30, 0.81]	0.006	1.55
Arbidol/ LPV/r vs. LPV/r					

Analysis	No. of studies	Sample size	Pooled estimate (%95CI)	P	Heterogeneity
Negative rate of PCR on 7 days	2	117	2.06 [1.13, 3.76]	0.02	0.01
Negative rate of PCR on 14 days	3	193	0.99 [0.55, 1.80]	0.99	9.44
Negative conversion time	3	229	2.21 [-0.13, 4.54]	< 0.00001	6.61
Hospital stay	2	145	1.51 [-3.94, 6.97]	0.59	6.46
Imrovement at CT on 7 days	2	117	1.05 [0.20, 5.50]	0.96	6.99
Arbidol vs. Arbidol/IFN					
Negative conversion time	2	291	-0.99 [-16.67, 14.69]	0.90	715.70
Arbidol/IFN vs. Arbidol					
Negative conversion time	2	194	2.31 [-7.78, 12.40]	0.65	28.11

Figures

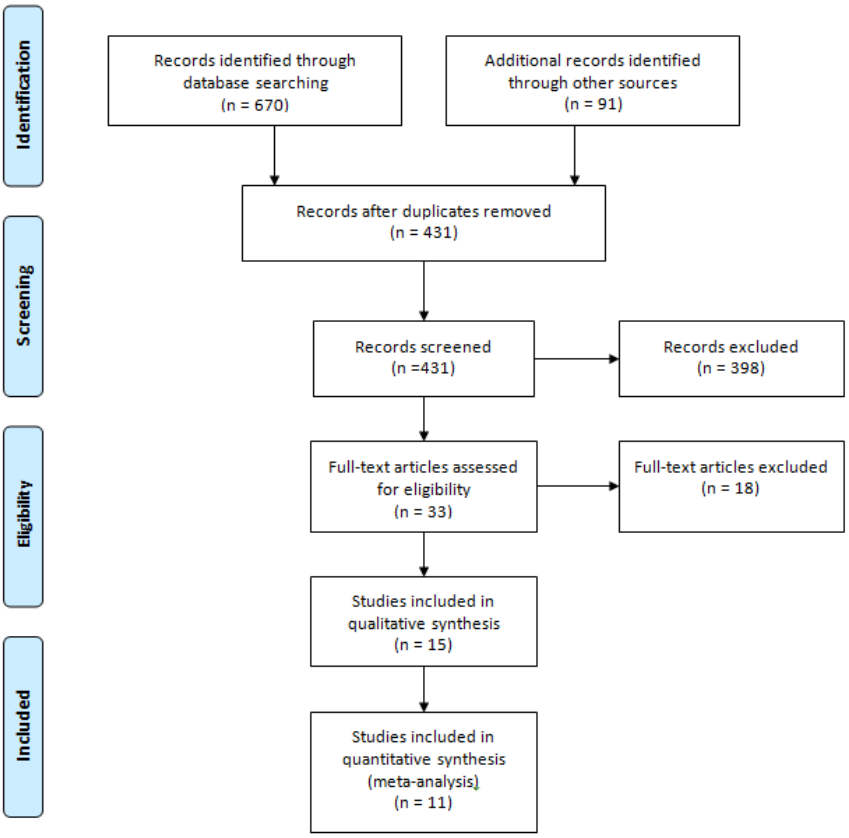
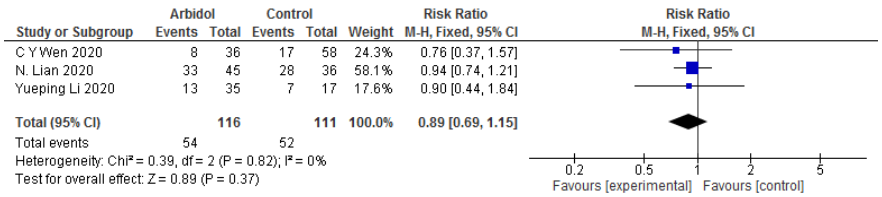
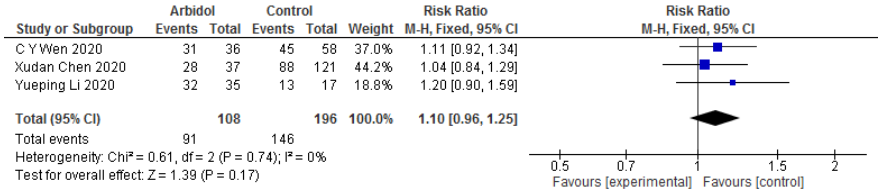


Fig 1. Study flow diagram

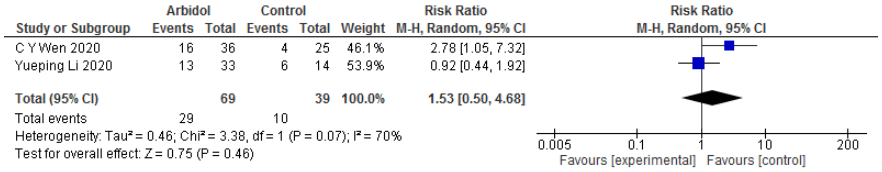
A. Negative rate of PCR on 7 days



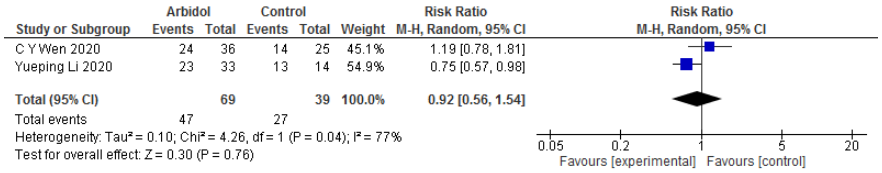
B. Negative rate of PCR on 14 days



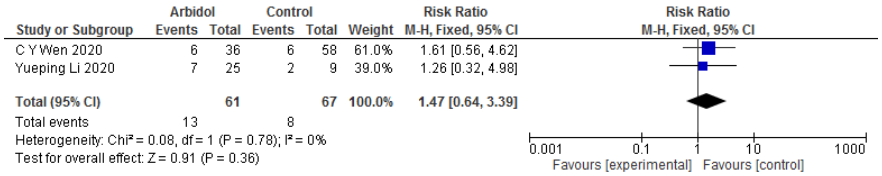
C. Rate of improvement at chest CT on 7 days



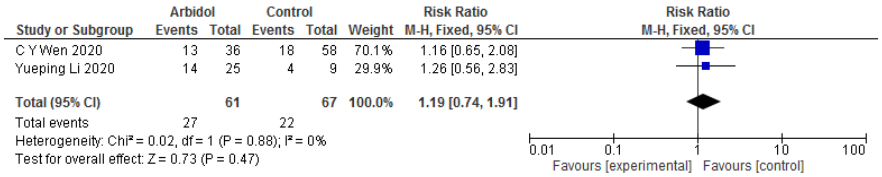
D. Rate of improvement at chest CT on 14 days



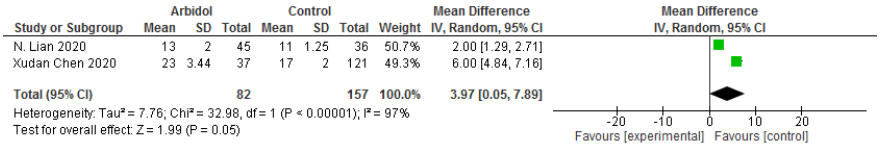
E. Rate of cough alleviation on 7 days



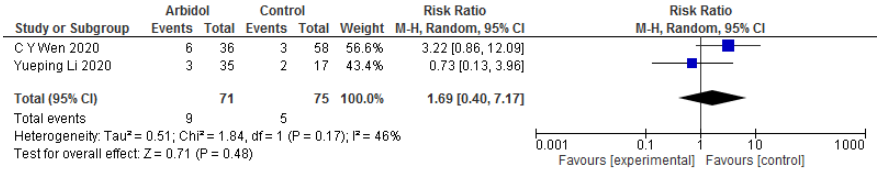
F. Rate of cough alleviation on 14 days



G. Hospital stay



H. Disease progression



I. Negative conversion time

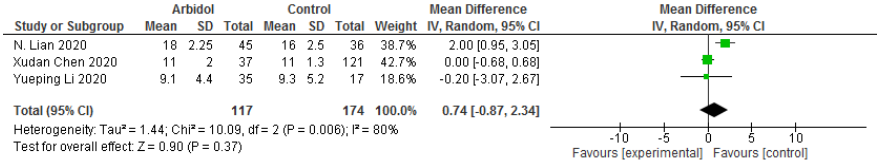


Fig 2 Forest plot of Arbidol vs. control

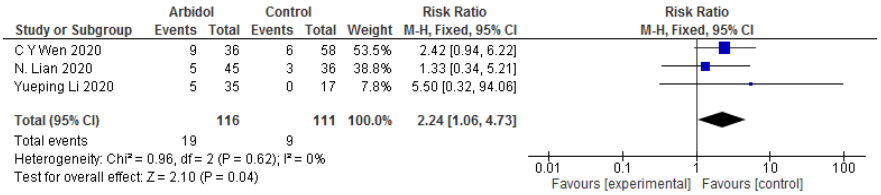


Fig 3 Forest plot of Arbidol vs. control for adverse events