

# Favipiravir versus other antiviral or standard of care for COVID-19 treatment: A rapid systematic review and meta-analysis

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## Research

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# Abstract

## Background

The coronavirus, cause of COVID-19 is an enveloped, RNA virus that utilizes an enzyme RNA dependent RNA polymerase for its replication. Favipiravir (FVP) triphosphate, a purine nucleoside analog, inhibits that enzyme. We have conducted this systematic review and meta-analysis on efficacy and safety of drug FVP as a treatment for COVID-19.

## Methods

Databases like Pubmed, Medline, Google Scholar, preprint sites, and clinicaltrials.gov were searched. Studies including FVP along with the standard of care (SOC) were taken in the treatment arm and SOC including other antivirals, and supportive care as control arm. Quantitative synthesis done using RevMan 5.4. Clinical improvement, negative conversion of reverse transcription-polymerase chain reaction (RT-PCR), adverse effects, and oxygen requirement were studied.

## Results

We identified a total of 824 studies after electronic database searching. Five in qualitative studies and three studies in quantitative synthesis meet the criteria. There was a significant clinical improvement on FVP arms on 14th day compared to control arms (RR 1.41, 1.10–1.80). Clinical deterioration rates was significantly unlikely in FVP group (OR 0.21, 0.08–0.58) at the endpoint of study. The meta-analysis showed no significant differences between two arms on virological clearance (Day 14: RR 1.03, 0.64–1.67), oxygen requirement (OR 0.47, 0.21–1.04), and adverse effects (OR 0.42, 0.03–6.05). There are 25 Randomized controlled trials (RCTs) registered in different parts of the world focusing FVP for COVID-19 treatment.

## Conclusion

There is significant clinical and radiological improvement following treatment with FVP in comparison to the standard of care with no significant differences on virological clearance, oxygen support requirement and side effect profile.

## 1. Background

The outbreak of a novel coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) started in Wuhan, China, in late December 2019. The COVID-19 caused by such virus was declared a global pandemic by the WHO on 11 March 2020 [1]. The number of cases and mortality that the virus has claimed around the globe is astronomical. As of 04 July 2020, the number of confirmed cases and deaths reported has reached 10,922,324 and 523,011 respectively [2]. This virus is getting transmitted mainly via respiratory tracts by droplets or respiratory secretions. The disease is characterized by asymptomatic to flu like mild respiratory symptoms including shortness of breath (SOB) leading to pneumonia, acute respiratory distress syndrome (ARDS), and even multiple organ dysfunction in severe cases [3]. The coronavirus is an enveloped, non-segmented positive-sense RNA virus that utilizes an enzyme RNA dependent RNA polymerase (RdRp) for its replication which could be a potential target for the treatment development [4].

The road to discover effective prophylaxis and treatment is still an ongoing process. Numerous trials of medications of different categories have been conducted but none have succeeded to show promising results for effective treatment [5, 6]. Some of the repurposed drugs are being utilized along with supportive care for the management of COVID-19 in different clinical settings.

Favipiravir (FVP) triphosphate, a purine nucleoside analog, competitively inhibits the enzyme RdRp. It has shown activity against influenza viruses, RNA viruses associated with viral hemorrhagic fever, and even against SARS-CoV-2 in vitro [7]. The evidence regarding FVP is relatively low as there have only been a handful of studies regarding its efficacy and safety among COVID-19 patients. We conducted this systematic review and meta-analysis to evaluate the efficacy and safety of drug FVP as a treatment for COVID-19.

## **2. Objective**

To determine the clinical improvement following treatment with FVP in cases of COVID-19, duration and percentage negative conversion of RT-PCR following treatment, adverse effects that were seen during treatment, oxygen requirement, and intubation and mechanical ventilation requirement following treatment.

## **3. Methods**

We used PRISMA for the systematic review of available literature [8].

### **3.1. Criteria for considering studies for this review**

#### **3.1.1. Types of studies**

We included studies that were done to determine the safety and efficacy of FVP along with the standard of care (SOC) for COVID-19 diagnosed cases based on guidelines in comparison to control arm receiving standard of care alone. All studies where FVP was used in the management of COVID-19 patients were included in qualitative analysis.

#### **3.1.2. Types of participants**

The studies had patients with COVID-19 diagnosed as per guidelines who were enrolled either in FVP and SOC compared to standard of care alone in quantitative analysis.

#### **3.1.3. Types of interventions**

FVP along with the SOC was taken in the treatment arm and SOC alone in the control arm. SOC included other antivirals, respiratory support, antibiotics, immunomodulators, and herbal medicines.

#### **3.1.4. Types of outcome measures**

Our outcomes were clinical improvement following treatment with FVP in cases of COVID-19; negative conversion of RT-PCR; adverse effects that were seen during treatment; oxygen requirement and mechanical ventilation requirement were outcomes of interest.

#### **3.1.5. Outcomes**

The parameters for clinical improvement were symptomatic improvement and radiological progression (pneumonia resolution), and clinical deterioration at usually 7 and 14 days after treatment between treatment and control arm. We also compared overall adverse effects occurred during treatment and respiratory support requirement between the treatment and control arm. We also compared time to negative RT-PCR and the percentage of negative RT-PCR at day 7 and 14 following treatment.

### **3.2. Search methods for identification of studies**

Studies were independently searched by two reviewers (DBS and PB) using COVIDENCE and data was extracted for quantitative and qualitative synthesis. The conflicts were resolved to take the opinion of the third reviewer (NP).

Assessment of bias and cross-checking of selected studies was done by another reviewer (SK).

## 3.2.1. Electronic searches

We have included the electronic search strategy in **supplementary file 1**.

## 3.3. Data collection and analysis

Databases like Pubmed, Medline, Google Scholar, Researchsquare, Medrxiv, and clinicaltrials.gov were searched. We decided to include preprints because the studies on FVP are actively ongoing and very few papers are out. We extracted data for quantitative synthesis and analyzed it using RevMan 5.4.

### 3.3.1. Selection of studies

We included RCTs, observational studies, and case series for our qualitative analysis in which FVP was used in the treatment of COVID-19 patients. We included studies with treatment arm in which patients received FVP and SOC in the treatment arm and SOC alone in the control arm for quantitative analysis. Studies lacking control arms were excluded. Reviews, protocols, in-vitro studies, and letters to editors were also excluded.

### 3.3.2. Data extraction and management

We evaluated the quality of the studies and included the outcome of interest in the quantitative synthesis.

### 3.3.3. Assessment of risk of bias in included studies

We used the Cochrane risk of bias (ROB) tool to analyze the risk of bias shown in Fig. 1 [9]. We used the NHLBI (National Heart, Lung, and Blood Institute) quality assessment tools (**Supplementary file 2**) to assess the risk of bias in observational studies and case series (Table 1) [10]. We used the RevMan 5.4 for the creation of risk-of-bias plots.

Table 1  
NHLBI assessment of observational studies and case series

Study	Study type	Score	Percentage	Quality
Rattanaumpawan et al [11]	Retrospective observational study	8/14	57.1%	Fair
Irie et al [12]	Case series	6/9	66.6%	Good
Good if they fulfilled 60–100% of the tool items, Fair if 50–59% or Poor if 0–49%				

Table 1: NHLBI assessment of observational studies and case series

### 3.3.4. Assessment of heterogeneity

We assessed the heterogeneity using the I-squared ( $I^2$ ) test. We used the Cochrane Handbook for Systematic Reviews of Interventions for interpretation of  $I^2$  test done as follows based on “0–40%: might not be important; 30–60% may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100%: considerable heterogeneity [13]. The importance of the observed value of  $I^2$  depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P-value from the chi-squared test, or a confidence interval for  $I^2$ ).”

### 3.3.5. Assessment of reporting biases

We assessed the reporting bias through predetermined outcome reporting documentation.

### 3.3.6. Data synthesis

We did a statistical analysis using RevMan 5.4 software. We used Risk Ratio (RR)/ Odds Ratio (OR) for outcome estimation whenever appropriate with 95% Confident Interval (CI). We used the fixed/random-effects model as per the heterogeneities. We assessed the heterogeneity using the  $I^2$  test, and we used the fixed/random-effects model for the pooling of studies. We analyzed the mean differences among the two groups for the duration of virological clearance using the median, sample size, and inter-quartile range when mean and standard deviation was not provided in the study [14].

### **3.3.7. Subgroup analysis and investigation of heterogeneity**

In the case of heterogeneity, we tried the inverse variance, random-effect model. We presented Forest plots to visualize the degree of variation between studies.

### **3.3.8. Sensitivity analysis**

For sensitivity analysis, we examined the effect of study based on their type (RCT and non-RCT) by excluding non-RCT studies and re-running the analysis to see for any differences.

## **4. Results**

### **4.1. Qualitative synthesis**

We identified a total of 824 studies after electronic database searching. After the removal of 96 duplicates, the title and abstracts of 728 studies were screened. We excluded 702 studies and 26 articles were assessed for full-text eligibility. A total of 21 articles were excluded for definite reasons. We included 5 studies in our qualitative study (Fig. 2). The summary of 5 studies is discussed in Table 2.

Table 2  
Qualitative synthesis of selected studies

Study, Year	Population	Intervention	Comparator	Outcome
Cai et al [15] 2020, Open label controlled study, China	Total: – 80 T: - 35 C: – 45 Sex: F = 45, M = men (35 of 80) History: Median age (IQR) 47 (35.75–61) Inclusion criteria: • Aged 16–75 years old; nasopharyngeal swabs samples tested positive for the novel coronavirus RNA • Duration from disease onset to enrolment was less than 7 d • willing to take contraception during the study and within 7 d after treatment • no difficulty in swallowing the pills. Exclusion: • Severe clinical condition (meeting one of the following criteria) i) Resting respiratory rate greater than 30 per minute ii) Oxygen saturation below 93%, oxygenation index < 300 mm Hg iii) Respiratory failure, shock, and/or combined failure of other organs that required ICU monitoring and treatment) • Chronic liver and kidney disease and	<b>Treatment group</b> FPV was 1600 mg twice daily on Day 1 and 600 mg twice daily on days 2–14. Medications were given till viral clearance was confirmed or 14 days had passed. Patients received IFN- a1b 60 mg twice daily by aerosol inhalation.	<b>Control group</b> LPV/RTV was LPV 400 mg/RTV 100 mg twice daily. Medications were given till viral clearance was confirmed or 14 days had passed. Patients received IFN- a1b 60 mg twice daily by aerosol inhalation.	Median time of viral clearance T: 4 d (IQR:2.5– 9) C: 11 d (IQR:8– 13) D8: RT-PCR negative for viral clearance T:26/35 C:17/45 D16: RT-PCR negative for viral clearance T:33/35 C:33/45 CT improvement D4: T:8/35; C:8/45 D9: T:18/35; C:16/45 D14 T:32/35; C:28/45 CT worse D14 T:1/35 C:9/45 Total number of adverse reactions T:4/35

Abbreviations: - ALT: Alanine Transaminase AST: Aspartate Transaminase C: Control COPD: Chronic Obstructive Pulmonary Disease D: Day DM: Diabetes Mellitus FPV: Favipiravir F: Female HIV: Human Immunodeficiency Virus HTN: Hypertension ICU: Intensive care unit IQR: Interquartile range M: Male MKD: Mean Dose per Kg N: Total number of patients LPV: Lopinavir RNA: Ribonucleic acid RT-PCR: Reverse Transcription-Polymerase Chain Reaction RTV: Ritonavir SARS: Severe Acute Respiratory Syndrome T: Treatment

Study, Year	Population	Intervention	Comparator	Outcome
	reaching end stages <ul style="list-style-type: none"> <li>• Previous history of allergic reactions to FPV or LPV/RTV</li> <li>• Pregnant or lactating women</li> <li>• Women of childbearing age with a positive pregnancy test, breastfeeding, miscarriage, or within 2 weeks after delivery; and participated in</li> <li>• Another clinical trial against SARS-CoV-2 treatment currently or in the past 28 d</li> </ul>			C:25/45

Abbreviations: - ALT: Alanine Transaminase AST: Aspartate Transaminase C: Control COPD: Chronic Obstructive Pulmonary Disease D: Day DM: Diabetes Mellitus FPV: Favipiravir F: Female HIV: Human Immunodeficiency Virus HTN: Hypertension ICU: Intensive care unit IQR: Interquartile range M: Male MKD: Mean Dose per Kg N: Total number of patients LPV: Lopinavir RNA: Ribonucleic acid RT-PCR: Reverse Transcription-Polymerase Chain Reaction RTV: Ritonavir SARS: Severe Acute Respiratory Syndrome T: Treatment

Study, Year	Population	Intervention	Comparator	Outcome
Lou et al [16] 2020, Open-label RCT, China	Total: 29 T = 9 and C = 10 T = FPV and C = Control Sex: F = 5, M = 14 History: Median age (SD) T = 58.0 (8.1); C = 46.6 (14.1) Inclusion: All RT-PCR diagnosed Exclusion: Patients who dint complete the dosage of the medication Previous history of malignancy, COPD, renal insufficiency and hepatic insufficiency	<b>Treatment group</b>  Baloxavir marboxil or FVP to the current standard antiviral  treatment was randomly allocated (1:1:1)  <b>FVP group:</b> FVP was used in combination with the existing antiviral treatment. The first dose was 1600 mg or 2200 mg orally, followed by 600 mg each time, three times a day, and the duration of administration was not more than 14 days  <b>Baloxavir group: -</b>  The dose was 80 mg OD on Day 1 and 4 and if patients are positive it can be given on Day 7 but no more than 3 doses should be given  Both groups received existing antiviral treatment including lopinavir/ritonavir (400 mg/100 mg, twice a day orally) or 8 darunavir/cobicistat (800 mg/150 mg, four times a day orally) and arbidol (200 mg, thrice a day orally ) along with interferon-alpha inhalation	<b>Control group</b>  Patients received existing antiviral treatment including lopinavir/ritonavir (400 mg/100 mg, twice a day orally) or 8 darunavir/cobicistat (800 mg/150 mg, four times a day orally) and arbidol (200 mg, thrice a day orally ) along with interferon-alpha inhalation.	Viral negative in Day 7 T: 4/9 C: 5/10  Viral negative in Day 14 T: 7/9 C: 10/10  Clinical improvement Day 14 T: 5/9 C: 5/10 Day 7 T: 2/9 C: 1/10 D14 Discharge T: 4/9 C: 4/10  Time to clinical improvement - median days (IQR) T:14 (6–38) C: 15 (6–24)  Time to viral negative-median days (IQR) T: 9 (2–34) C: 9 (1–13) D14 NMV OR Oxygen support T: 3/9 C: 4/10

Abbreviations: - ALT: Alanine Transaminase AST: Aspartate Transaminase C: Control COPD: Chronic Obstructive Pulmonary Disease D: Day DM: Diabetes Mellitus FPV: Favipiravir F: Female HIV: Human Immunodeficiency Virus HTN: Hypertension ICU: Intensive care unit IQR: Interquartile range M: Male MKD: Mean Dose per Kg N: Total number of patients LPV: Lopinavir RNA: Ribonucleic acid RT-PCR: Reverse Transcription-Polymerase Chain Reaction RTV: Ritonavir SARS: Severe Acute Respiratory Syndrome T: Treatment

Study, Year	Population	Intervention	Comparator	Outcome
Chen et al [17] 2020, RCT, China	<p>Total: 236</p> <p>T: 116 C: 120</p> <p>Inclusion</p> <ul style="list-style-type: none"> <li>• Age 18 years or older</li> <li>• Voluntarily provided informed consent</li> <li>• Initial symptoms were within 12 days</li> </ul> <p>• Diagnosed as COVID-19</p> <p>pneumonia</p> <p>Exclusion</p> <ul style="list-style-type: none"> <li>• Allergic to FVP or Arbidol</li> <li>• Increased ALT/AST (&gt; 6x upper limit of normal range) or with chronic liver disease (cirrhosis at grade Child-Pugh C)</li> <li>• Severe/critical patients whose expected survival time were &lt; 48 hrs</li> <li>• Pregnant female</li> <li>• HIV infected</li> <li>• Considered unsuitable by researchers for patient's interest</li> </ul>	<p><b>Treatment Group</b></p> <p>Patients received FVP (1600 mg, twice the first day followed by 600 mg, twice daily, for the following days plus standard care for 7 days.</p>	<p><b>Control group</b></p> <p>Patients received Arbidol (200 mg, three times daily) plus standard of care for 7 days.</p> <p>Standard of cure included traditional Chinese herbal medicine, antibiotics, additional antiviral treatment, immunomodulatory drugs, steroids, psychotic drugs, nutrition support, cardiovascular drugs, supportive oxygen, noninvasive positive pressure ventilation (NPPV) or invasive ventilation</p>	<p>D7 Clinical Recovery</p> <p>T: 71/116 C: 62/120</p> <p>Clinical deterioration (new dyspnea)</p> <p>T: 4/116 C: 14/120</p> <p>D7 NMV OR Oxygen support</p> <p>T: 27/120 C:21/116</p> <p>Total number of adverse reactions</p> <p>T:37/116 C:28/120</p> <p>Respiratory failure</p> <p>T: 1/116 C: 4/120</p> <p>No mortalities</p>

Abbreviations: - ALT: Alanine Transaminase AST: Aspartate Transaminase C: Control COPD: Chronic Obstructive Pulmonary Disease D: Day DM: Diabetes Mellitus FVP: Favipiravir F: Female HIV: Human Immunodeficiency Virus HTN: Hypertension ICU: Intensive care unit IQR: Interquartile range M: Male MKD: Mean Dose per Kg N: Total number of patients LPV: Lopinavir RNA: Ribonucleic acid RT-PCR: Reverse Transcription-Polymerase Chain Reaction RTV: Ritonavir SARS: Severe Acute Respiratory Syndrome T: Treatment

Study, Year	Population	Intervention	Comparator	Outcome
Rattanaumpawan et al [11] 2020, Observational study, Thailand	<p>Total: 247</p> <p>T: 63 C: 184</p> <p>Inclusion:</p> <p>Patients aged at least 18 years who had RT-PCR-confirmed SARS-CoV-2 based on a respiratory specimen (nasopharyngeal, oropharyngeal, sputum, endotracheal aspirate, or bronchoalveolar lavage sample) and received at least one dose of FVP.</p> <p>Exclusion:</p> <p>Patients who expired or were discharged within 24 hrs of hospital stay</p>	<p><b>Treatment group</b></p> <p>Patients received the median loading dose of FVP of 47.4 (29.1–71.1) MKD along with the standard of cure, and one-third of 176 enrolled patients (33.3%) received a loading dose of <math>\leq 45</math> MKD.</p> <p>The median maintenance 177 dose of FVP was 17.9 (10.9–26.7) MKD, and 76.2% of the subjects received a 178 maintenance dose of <math>\leq 15</math> MKD.</p> <p>The median duration of FVP therapy was 12 (2–17) days</p> <p>Standard of cure includes protease inhibitors, hydroxychloroquine, azithromycin, steroid, respiratory support, and tocilizumab</p>	<p><b>Control group</b></p> <p>Patients received standard of cure including protease inhibitors, hydroxychloroquine, azithromycin, steroid, tocilizumab, and respiratory support.</p>	<p>Outcomes of treatment groups have been only reported. <b>N = 63</b></p> <p>Clinical improvement</p> <p>D7: 42/63</p> <p>No requirement of oxygen supplementation: 25/63</p> <p>D14: 54/63</p> <p>No requirement of oxygen supplementation: 27/63</p> <p>D28: 57/63</p> <p>No requirement of oxygen supplementation: 27/63</p> <p>Mortality</p> <p>D14: 1</p> <p>D28: 3</p> <p>Adverse drug reaction</p> <p>39/63</p> <p>Most common diarrhea (34) and hepatitis (4)</p>

Abbreviations: - ALT: Alanine Transaminase AST: Aspartate Transaminase C: Control COPD: Chronic Obstructive Pulmonary Disease D: Day DM: Diabetes Mellitus FVP: Favipiravir F: Female HIV: Human Immunodeficiency Virus HTN: Hypertension ICU: Intensive care unit IQR: Interquartile range M: Male MKD: Mean Dose per Kg N: Total number of patients LPV: Lopinavir RNA: Ribonucleic acid RT-PCR: Reverse Transcription-Polymerase Chain Reaction RTV: Ritonavir SARS: Severe Acute Respiratory Syndrome T: Treatment

Study, Year	Population	Intervention	Comparator	Outcome
Irie et al [12] 2020, Case Series, Japan	Total: 7 M: 5 F: 2	Patients were given 1600 mg FPV on day 1 and 600 mg from day 2–5		Clinical improvement 3/7
	Comorbidities HTN: 3			At Day 7 1/7
	DM: 2 Hyperuricemia: 2 Others included BPH, gout, and fibroid			No requirement for mechanical ventilation: 1/7
	Inclusion: Critically ill patients admitted to ICU under mechanical ventilation			At Day 14 3/7
				Weaned from mechanical ventilation: 3/7
				No oxygenation support: 2/7
				Adverse effect 1/7 (Increase in transaminase)

Abbreviations: - ALT: Alanine Transaminase AST: Aspartate Transaminase C: Control COPD: Chronic Obstructive Pulmonary Disease D: Day DM: Diabetes Mellitus FPV: Favipiravir F: Female HIV: Human Immunodeficiency Virus HTN: Hypertension ICU: Intensive care unit IQR: Interquartile range M: Male MKD: Mean Dose per Kg N: Total number of patients LPV: Lopinavir RNA: Ribonucleic acid RT-PCR: Reverse Transcription-Polymerase Chain Reaction RTV: Ritonavir SARS: Severe Acute Respiratory Syndrome T: Treatment

Table 2: Qualitative synthesis of selected studies

## 4.2. Quantitative analysis

Three studies meet the criteria and included in the quantitative synthesis. In the present meta-analysis, we have compared findings among randomized studies and control studies to extract outcome on virological clearance, improvement or deterioration among FVP group in comparison to COVID-19 cases getting other antivirals or SOC, duration to virological clearance, the requirement of oxygen support and adverse effects.

### 4.2.1. FVP versus other antivirals or SOC only; effectiveness

Among treatment group FVP in addition to SOC versus other antivirals or SOC we have compared the duration of virological clearance (negative RT-PCR) and radiological/ clinical improvement.

### **A. Virological clearance**

The meta-analysis of risk ratios (RR) for FVP in addition to SOC effectiveness compared with other antivirals or SOC using random error model among randomized and non-randomized studies showed that there were no significant differences between two arms (Day 7: RR 1.49, 95% CI 0.71 to 3.13; Day 14: RR 1.03, 95% CI 0.64 to 1.67). Also, there is no significant risk difference (RD) for virological cure between two groups FVP in addition to SOC versus other antivirals or SOC (Day 7: RD 0.20, 95% CI -0.20 to 0.61; Day 14: RD 0.01, 95% CI -0.41 to 0.43) (Fig. 3). For heterogeneity, the subgroup assessment inverse variance method used and showed no significant changes noted (**Supplement file 3/** Fig. 1).

### **B. Clinical/ CT improvement**

Among three studies; two reported clinical and one reported CT improvement, overall risk ratios (RR) for FVP in addition to SOC effectiveness compared with other antivirals or SOC alone using random-effect model showed that there was a significant improvement on FVP arms on 14th day though that on 7th day is not statistically significant (Day 7: RR 1.17, 95% CI 0.96 to 1.44; Day 14: RR 1.41, 95% CI 1.10 to 1.80). Also there is similar findings on risk difference (RD) between two groups for improvement (Day 7: RD 0.08, 95% CI -0.02 to 0.19; Day 14: RD 0.25, 95% CI 0.08 to 0.41) (Fig. 4).

Clinical improvement on 7th day among two randomized controlled trials after excluding non-randomized study by Cai Q et al [15] showed slight increased improvement rate but not statistically significant (RR 1.11, 95% CI 0.89 to 1.39; RD 0.06, 95% CI -0.06 to 0.18) (**Supplement file 3/** Fig. 2)

## **4.2.2. FVP versus other antivirals: clinical deterioration**

The meta-analysis on clinical deterioration rate at the point of concluding studies showed clinical deterioration is significantly unlikely in FVP treatment group than other antiviral agents (OR 0.21, 95% CI 0.08 to 0.58; participants = 316; studies = 2;  $I^2 = 0\%$ ) (Fig. 5).

## **4.2.3. FVP group versus other antivirals or SOC group: Oxygen support or non-invasive ventilation**

Meta-analysis on oxygen support requirement and non-invasive mechanical ventilation among included randomized studies showed decreased odds of oxygen support among FVP group but it is not statistically significant (OR 0.47, 95% CI 0.21 to 1.04; participants = 228; studies = 2;  $I^2 = 0\%$ ) (Fig. 6).

## **4.2.4. Adverse effects**

Meta-analysis comparing adverse effects between treatment and control group showed less odds for adverse effect in treatment arm but of no statistical significance (OR 0.42, 95% CI 0.03 to 6.05; participants = 316; studies = 2;  $I^2 = 94\%$ ) (Fig. 7)

## **4.2.5. Duration to convert negative RT-PCR**

Our meta-analysis on negative conversion of RT-PCR demonstrated approximately 5 days (MD -5.16, 95% CI -6.95 to -3.37; participants = 99; studies = 2;  $I^2 = 45\%$ ) earlier on treatment with FVP group (Fig. 8). Being data is subject to moderate heterogeneity sensitivity assessment using the random-effect model showed no significance (MD -2.16, 95% CI -13.28 to 8.97) so this finding needs to be confirmed by further randomized studies (**Supplement file 3/** Fig. 3).

## 4.3 Clinical trials

Focusing on the safety and efficacy of FVP for COVID-19 treatment along with different parameters, there are 25 RCTs registered in different parts of the world as of 04 July 2020 (**Supplementary file 4**) [18]. Three of such trials have recently been completed from Egypt, Iran, and Turkey. Among the registered RCTs, 9 trials are recruiting participants, 9 trials have not yet started recruiting, and 4 trials are active but not recruiting participants. The withdrawn one trial has not been included in this calculation. According to the location provided in 23 trials, a maximum number of trials are regulated by Turkey followed by Egypt. The record of maximum and minimum enrollment is recorded from different studies in Turkey with 1000 and 18 participants, respectively.

## 5. Discussion

Our meta-analysis was focused on the assessment of the clinical outcome and adverse effects following therapy with FVP because it has emerged as one of the treatment repurposed for COVID 19. Although some promise has been shown by remdesivir and plasma therapy, the lack of highly efficacious and safe treatment for COVID 19 remains one of the biggest conundrums of the 21st century. Our study found that patients had statistically significant clinical improvement at 14th day (RR 1.41, 95% CI 1.10 to 1.80) following treatment with FVP. The clinical deterioration was found to be highly unlikely (OR 0.21, 95% CI 0.08 to 0.58) following treatment. There were no significant differences in viral clearance between two arms (Day 7: RR 1.49, 95% CI 0.71 to 3.13; Day 14: RR 1.03, 95% CI 0.64 to 1.67). The overall risk of adverse effects was lower compared to the standard of care but not statistically significant (OR 0.42, 95% CI 0.03 to 6.05). In general, there were tolerable minor side effects like diarrhea and an increase in transaminases and no serious life-threatening complications following FVP treatment. Because this is the first meta-analysis comparing the clinical outcome and adverse effects among patients receiving FVP compared to standard of care, we couldn't compare our findings with other meta-analyses.

Although good promise has been shown by FVP, additional randomized double-blind clinical trials are needed to give a definite opinion about the rationale of the use of the drugs. We could only include 3 studies for our quantitative analysis and among them also, one study was non-randomized. The sample size was small in our studies which decreases the power of our study. The duration of treatment and dosages were different among various studies in qualitative analysis. Two RCTs that we included for our analysis had a varied duration of treatment too. Lack of randomization may have led to selection bias in non-randomized studies. Blinding could not be applied to the studies leading to biases. Selective reporting may have been a problem in Chen's study because of the limited observation time frame. It is important to determine the appropriate dose and duration of treatment with FVP because low dose therapy is found to be a bad prognostic factor for clinical improvement and widespread variations in treatment duration among studies and lack of effective plasma concentrations of drug in critically ill patients [11, 12]. Because of the early evidence of potential benefits shown by this drug in clinical improvement as well as imaging improvement, it is necessary to conduct large scale prospective, double-blind randomized controlled trials to further increase the power of the study and eliminate biases so that definitive advice for treatment can be given in the coming days.

## 6. Conclusion

Our study concludes that patients had clinical and radiological improvement following treatment with FVP in comparison to the standard of care with no significant differences on virological clearance, oxygen support requirement and side effect profile. The results of ongoing clinical trials are to be waited to give a definite judgment on whether treatment with FVP is the best option among antiviral treatments for COVID 19. Till that time our meta-analysis support judicial use of FVP in clinical setting.

## Abbreviations

ALT: Alanine transaminase; ARDS:Acute respiratory distress syndrome; AST:Aspartate transaminase; C:Control; CI:Confidence interval; COPD:Chronic obstructive pulmonary disease; COVID-19:Coronavirus disease-19; D:Day; DM:Diabetes mellitus; F:Female; FVP:Favipiravir; HIV:Human immunodeficiency virus; HTN:Hypertension; I<sup>2</sup>:I-squared; ICU:Intensive care unit; IQR:Interquartile range; LPV:Lopinavir; M:Male; MKD:Mean dose per Kg; N:Total number of patients; NHLBI:National Heart, Lung, and Blood Institute; OR:Odds ratio; PRISMA:Preferred reporting items for systematic reviews and meta-analyses; RCTs:Randomized controlled trials; RdRp:RNA dependent RNA polymerase; ROB:Risk of bias; RR:Relative risk; RT-PCR:Reverse transcription-polymerase chain reaction; RTV:Ritonavir ; SARS-CoV-2:Severe acute respiratory syndrome coronavirus-2 ; SOB:Shortness of breath; SOC:Standard of care; T:Treatment

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable

### Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

DBS, PB, and SK contributed in concept and design, analysis, and interpretation of data. PBS, NP, and PR contributed in literature search, data extraction, review and assisted in analysis.

All authors were involved in drafting and revising the manuscript and approved the final version.

### Acknowledgements

Not applicable

## References

1. WHO. Novel Coronavirus – China. WHO. 2020. <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>. Accessed 5 Jul 2020.
2. WHO. Coronavirus (COVID-19). WHO. 2020. [https://covid19.who.int/?gclid=EAlaIqobChMI9ai8slOz6gIVzQorCh297QloEAAYASAAEgIQ7vD\\_BwE](https://covid19.who.int/?gclid=EAlaIqobChMI9ai8slOz6gIVzQorCh297QloEAAYASAAEgIQ7vD_BwE). Accessed 5 Jul 2020.

3. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). *Indian J Pediatr.* 2020 Apr;87(4):281–6.
4. Gaurav A, Al-Nema M. Polymerases of Coronaviruses: Structure, Function, and Inhibitors. *Viral Polymerases.* 2019. p. 271–300.
5. Yousefifard M, Zali A, Mohamed Ali K, Madani Neishaboori A, Zarghi A, Hosseini M, et al. Antiviral therapy in management of COVID-19: a systematic review on current evidence. *Arch Acad Emerg Med.* 2020;8(1):e45.
6. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020;323(18):1824–36. Available from: <https://doi.org/10.1001/jama.2020.6019>
7. Coomes EA, Haghbayan H. Favipiravir, an antiviral for COVID-19? *J Antimicrob Chemother.* 2020 Jul;75(7):2013–4.
8. Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P., ... & Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151(4):W-65.
9. Cochrane. RoB 2.0: A revised tool to assess risk of bias in randomized trials [webinar]. Cochrane Training. <https://training.cochrane.org/resource/rob-20-webinar>. Accessed 5 Jul 2020.
10. NHLBI. Study Quality Assessment Tools. National Heart, Lung, and Blood Institute (NHLBI). 2020. <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>. Accessed 5 Jul 2020.
11. Rattanaumpawan P, Jirajariyavej S, Lerdlamyong K, Palavutitotai N, Saiyarin J. Real-world Experience with Favipiravir for Treatment of COVID-19 in Thailand: Results from a Multi-center Observational Study. *medRxiv.* 2020; Available from: <https://www.medrxiv.org/content/early/2020/07/01/2020.06.24.20133249.1>
12. Irie K, Nakagawa A, Fujita H, Tamura R, Eto M, Ikesue H, et al. Pharmacokinetics of Favipiravir in Critically Ill Patients With COVID-19. *Clin Transl Sci [Internet].* n/a(n/a). Available from: <https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1111/cts.12827>
13. Cochrane. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Training. <https://training.cochrane.org/handbook>. Accessed 5 Jul 2020.
14. Wayback Machine [Internet]. Internet Archive. <https://web.archive.org/web/20181224162602/http://www.comp.hkbu.edu.hk/~xwan/median2mean.html>). Accessed 5 Jul 2020.
15. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Eng (Beijing, China).* 2020 Mar;
16. Lou Y, Liu L, Qiu Y. Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: an Exploratory Randomized, Controlled Trial. *medRxiv [Internet].* 2020; Available from: <https://www.medrxiv.org/content/early/2020/05/05/2020.04.29.20085761>.
17. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial [Internet]. *medRxiv;* 2020. Available from: <https://doi.org/10.1101/2020.03.17.20037432>
18. ClinicalTrials.gov. NIH U.S. National Library of Medicine. 2020. <https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=Favipiravir&cntry=&state=&city=&dist=&Search=Search>. Accessed 5 Jul 2020.

## Figures

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cai Q 2020	High risk	High risk	High risk	High risk	Low risk	Low risk	Unclear risk
Chen C 2020	Low risk	Unclear risk	High risk	High risk	High risk	High risk	Unclear risk
Lou Y 2020	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk

Figure 1

Risk of bias assessment of trials

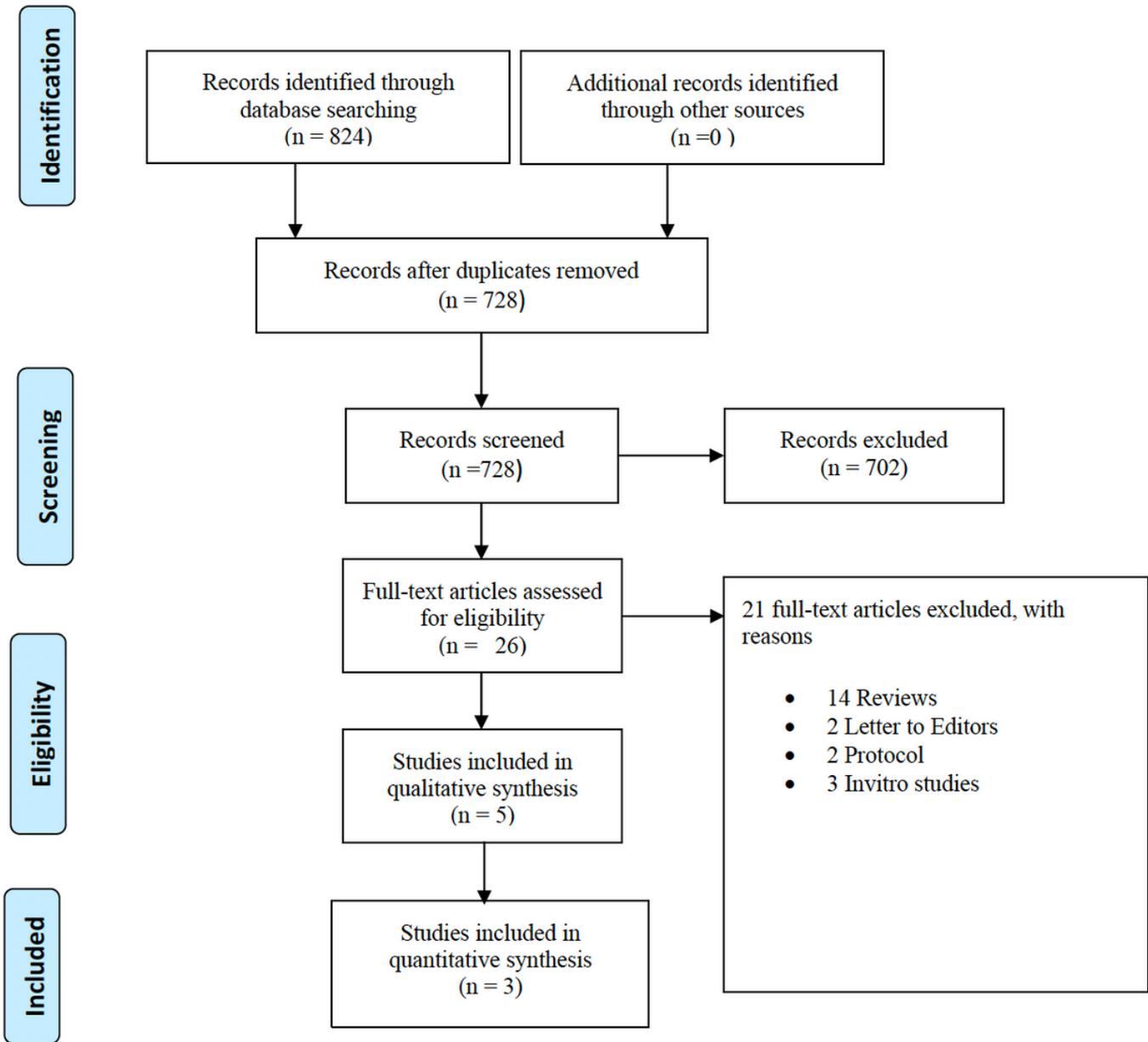
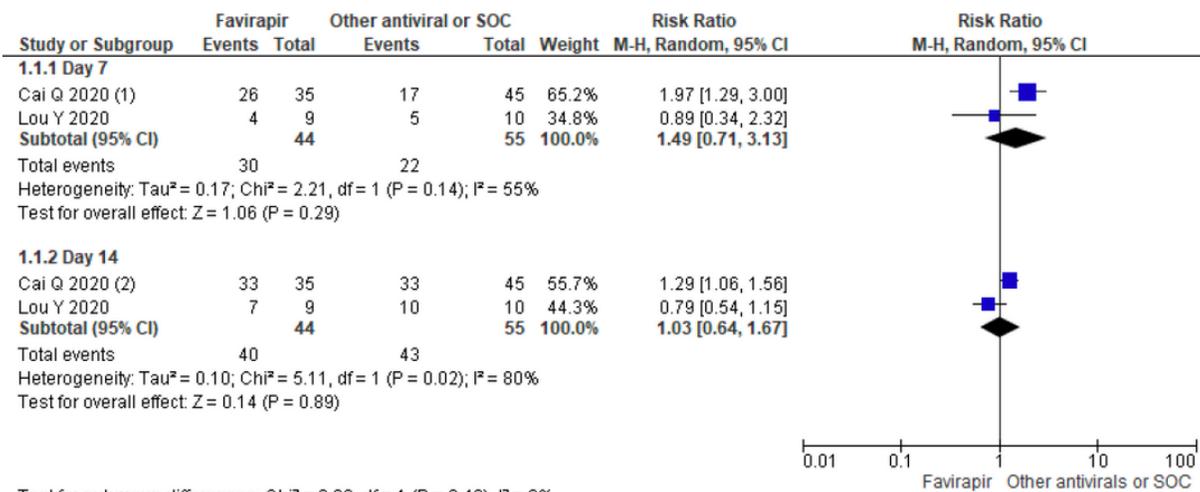


Figure 2

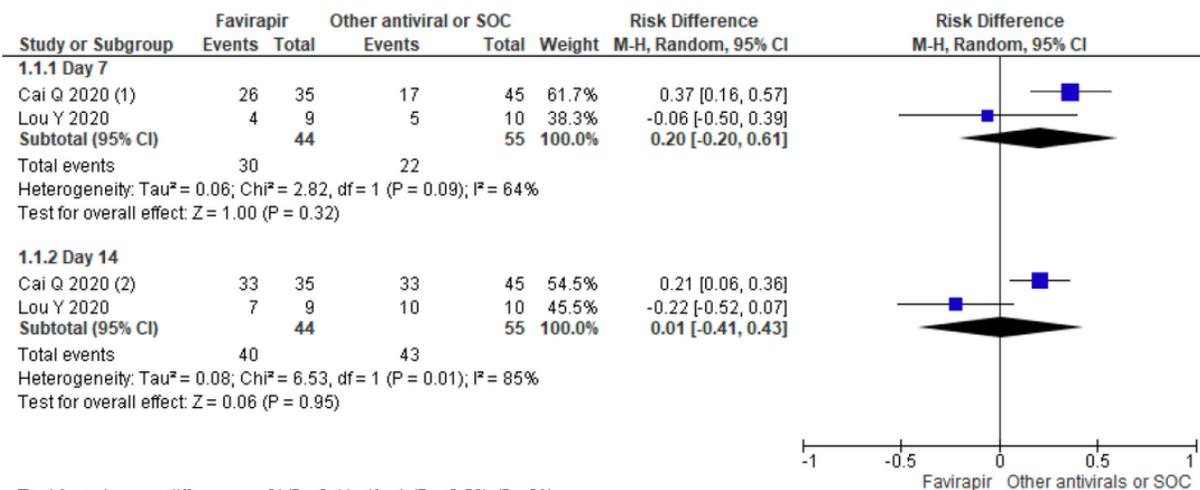
PRISMA 2009 flow diagram



Test for subgroup differences: Chi<sup>2</sup> = 0.66, df = 1 (P = 0.42), I<sup>2</sup> = 0%

Footnotes

- (1) Day 8 taken instead of day 7;
- (2) Day 16 taken as day 14



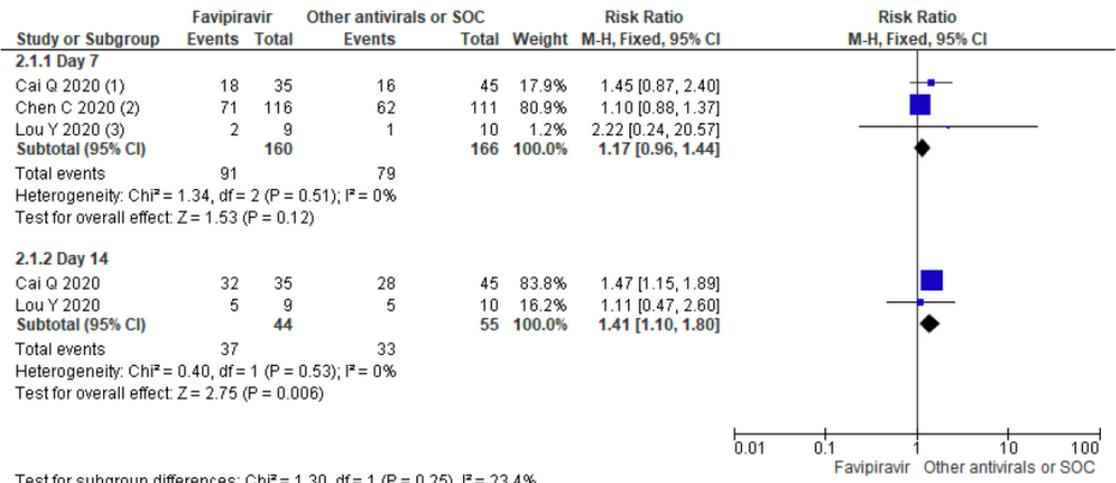
Test for subgroup differences: Chi<sup>2</sup> = 0.41, df = 1 (P = 0.52), I<sup>2</sup> = 0%

Footnotes

- (1) Day 8 taken instead of day 7;
- (2) Day 16 taken as day 14

**Figure 3**

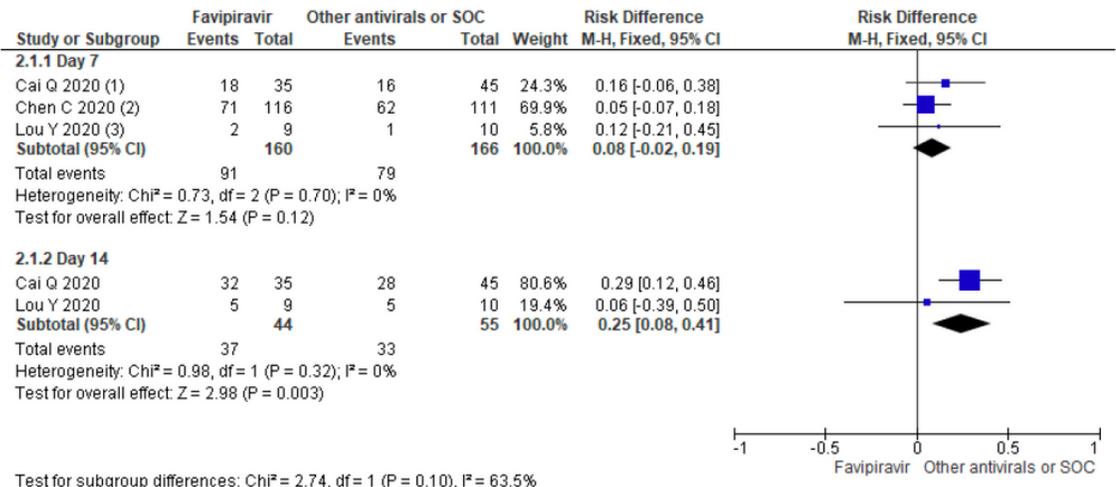
Forest plot for risk ratios and risk differences regarding FVP in addition to SOC effectiveness for virological clearance compared with other antivirals or SOC



Test for subgroup differences: Chi<sup>2</sup> = 1.30, df = 1 (P = 0.25), I<sup>2</sup> = 23.4%

**Footnotes**

- (1) Day 9 CT improvement
- (2) Clinical recovery
- (3) Clinical improvement



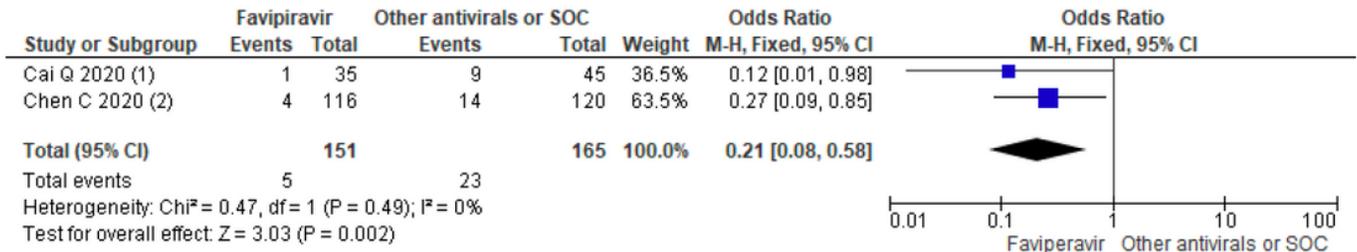
Test for subgroup differences: Chi<sup>2</sup> = 2.74, df = 1 (P = 0.10), I<sup>2</sup> = 63.5%

**Footnotes**

- (1) Day 9 CT improvement
- (2) Clinical recovery
- (3) Clinical improvement

**Figure 4**

Forest plot for risk ratios and risk differences regarding FVP in addition to SOC effectiveness for clinical improvement compared with other antivirals or SOC

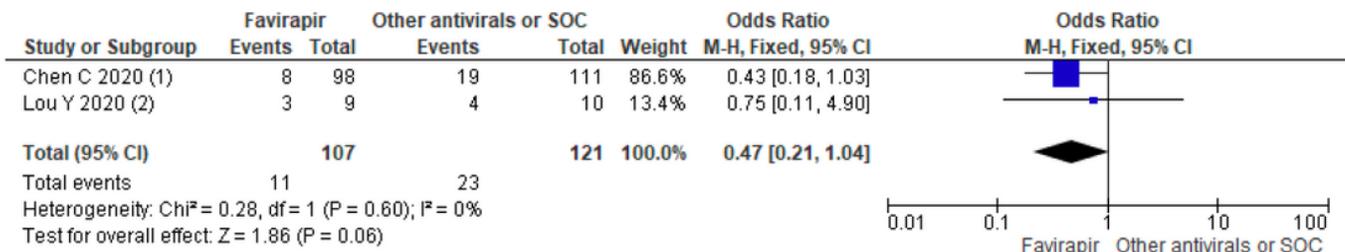


**Footnotes**

- (1) 1 Day 14 CT worsening
- (2) 2 Day 7 clinical deterioration (new dyspnea)

**Figure 5**

Forest plot for odds ratios regarding clinical deterioration among FVP group versus other antivirals

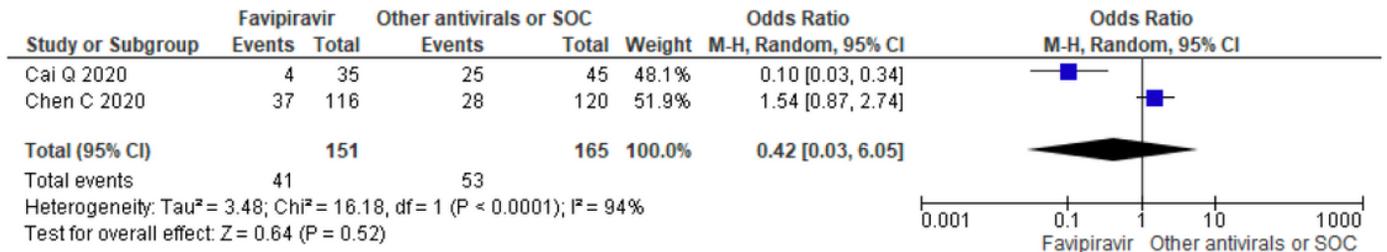


**Footnotes**

- (1) 1 Day 7 NMV or O2 support
- (2) 2 Day 14 O2 support

**Figure 6**

Forest plot for odds ratios requiring oxygen support or non-invasive ventilation among FVP group versus other antivirals or SOC group



**Figure 7**

Forest plot for odds ratios for adverse effects among FVP group versus other antivirals

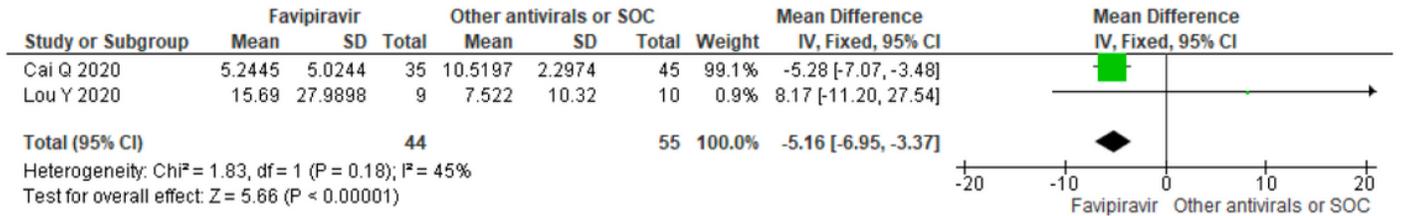


Figure 8

Forest plot of FVP in addition to standard of care or other anti-virals on negative conversion of RT-PCR

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaryfile5.Prismachecklist.docx](#)
- [Supplementaryfile4.ClinicaltrialsFavipiravir.docx](#)
- [Supplementaryfile3.Synthesis.docx](#)
- [Supplementaryfile2.NHLBIbias.docx](#)
- [Supplementaryfile1.Searchstratgey.docx](#)