

Coronavirus Pandemic

A systematic review and Bayesian network meta-analysis for comparative safety assessment of favipiravir interventions in hospitalized COVID-19 patients

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Abstract

Introduction: COVID-19 is a coronavirus-based infectious illness that was first detected at the end of 2019 in Wuhan, China. The novel virus induces severe acute respiratory syndrome (SARS-CoV-2) and has spread globally, resulting in an ongoing pandemic. There is still a lack of evidence for direct comparison of favipiravir therapy. Network meta-analysis (NMA), may incorporate direct and indirect comparisons in a pooled computation while depending on strong assumptions and premises. This study provides evidence-based recommendations on the safety of currently used clinical pharmacological treatments compared to favipiravir for COVID-19 patients.

Methodology: We conducted a systematic review and Bayesian NMA. We searched the primary databases and clinical trials center for reports of short-term, randomized controlled trials (RCTs) of favipiravir for COVID-19 treatment. The primary endpoints here considered were any adverse events observed or reported during the treatment cycle with estimates of odds ratio (OR) and 95% confidence interval (CI), until November 6, 2021.

Results: Between January 2020 and July 2021, 908 individuals were randomly assigned to one of the seven active prescription medication regimens or placebo in this study, generating seven direct comparisons on 12 data points. The safety of favipiravir over the four clinically efficacious monotherapies or combinations including tocilizumab, arbidol, lopinavir + ritonavir, and chloroquine remained unknown due to the lack of a significant difference and the limited sample size.

Conclusions: Overall, comparative rankings could assist doctors and guideline developers in decision-making. We have also concluded that the safety of favipiravir requires further attention.

Key words: COVID-19; favipiravir; safety; adverse events; network meta-analysis.

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Introduction

COVID-19, commonly known as SARS-CoV-2, was identified as a novel coronavirus in late 2019 and triggered an intercontinental respiratory illness outbreak [1], according to systematic evaluations, up to 40% of COVID-19 patients are asymptomatic; respiratory symptoms, cough, fever, tiredness, myalgia, and headache are the most often reported symptoms [2,3]. The new disease has resulted in worldwide health and economic calamity, affecting over 24 million people and resulting in over 5,000,000 fatalities in over 200 countries [4]. Since no specific antiviral medication has been approved to be used to treat patients with COVID-19, the use of one or a combination of the already available medications has become the foundation for the treatment of the novel disease.

Previous research has linked PsO patients who use biologics to an increased risk of SARS-CoV-2 infection

and hospitalization (unadjusted OR 3.43 [95% CI 2.25-5.73]) [5]. According to a retrospective study, a significant difference was also seen between SARS-CoV-2 infection and non-infection in patients undergoing chronic angiotensin II receptor blocker (ARB) medication (18.6% versus 9.5%, $p = 0.012$) [6]. In cells, favipiravir is phosphoribosylated to form favipiravir-RTP, which inhibits RdRp enzyme activity [7]. Four lopinavir structural analogues and one favipiravir structural analogue created through structural modification exhibited drug-forming characteristics that inhibit COVID-19 major protease (M pro) and RNA-dependent RNA polymerase (RdRp) [8]. This substance has a broad range of antiviral effects. It has been previously demonstrated that, in animals, the drug effectively acts against viruses, including the West Nile virus, the yellow fever virus, and the foot-and-mouth disease virus [9]. Favipiravir is

currently approved to treat COVID-19 patients in Japan and other countries [10–12]. However, many debates and concerns about its efficacy and safety have been aroused. A Series of RCTs have been conducted to verify the antiviral efficacy and overall safety [13,14]. An open-label randomized clinical trial found that favipiravir did not shorten the mean hospital stay significantly in SARS-CoV-2 treatment when compared to lopinavir/ritonavir (7.9 days [SD = 6] versus 8.1 days [SD = 6.5]) [15]. A historically controlled, single-arm proof-of-concept trial of Ebola virus disease found that, compared to individuals who started taking favipiravir within 72 hours of the first symptoms to those who did not use the medication, the RNA viral load levels and mortality rates were not significantly different [16]. Furthermore, the various mood disorders, depressive symptoms, and drug interactions that occur as a result of drug and vaccine use in the treatment of COVID-19 cannot be overlooked, and adjusting existing drug combinations or avoiding the use of certain drugs in specific COVID-19 patients may lead to additional research to identify strategies to manage psychiatric problems in this population [17–19].

Nonetheless, data on the safety of favipiravir in COVID-19 treatment are still very limited, considering the long-term prevention of emergent adverse effects and early mortality from medical reasons. Researchers and clinical experts should consider the risks of the side effects of drugs used to treat the new virus.

Clinical guidelines can be used as a basis for recommendations based on drug evidence. Still, these guidelines rarely rank drug efficacy in an effective way. Pharmaceutical companies and research institutions are frequently unmotivated to conduct extensive clinical studies comparing the effectiveness of multiple drugs due to limited resources and expenses. Unlike traditional pair-wise meta-analyses, which can only be used to compare therapies with direct evidence, a new statistical method known as NMA can combine direct and indirect comparisons in a single calculation [20], this technique may evaluate treatments with indirect evidence as well as using strong assumptions and premises. NMA can integrate currently available data to improve precision and visualize new ranking probabilities to inform clinical guidance [21]. In this study, we created an extensive network that includes all the currently available antiviral regimens to compare the safety of favipiravir regimens in COVID-19 patients based on the results of a series of RCTs.

Methodology

Search strategy and selection criteria

With the commercialization of new medications and the publication of an increasing number of clinical trials each year, an updated and enlarged systematic review and network meta-analysis are required to synthesize the data in this critical clinical sector. Between January 10, 2020, and July 10, 2021, we have looked into Pubmed, the Cochrane Central Register of Controlled Trials, the International Clinical Trials Registry Platform, MedRxiv, and ClinicalTrials.gov for relevant RCTs of potential medicines pharmaceuticals for hospitalized patients with COVID-19, with no language constraints. All appropriate pharmaceutical firms and authors were asked to fill reporting gaps in the original studies or to provide additional information for previously unreported data. We used the search keywords "Covid-19*" OR "corona virus*" AND "favipiravir*" OR "Avigan*" AND "RCT*" OR "trial*" OR "randomized controlled trials*" together with the names of all clinically used antiviral drugs following the PRISMA NMA checklist [22] (Supplementary Table 2).

We included double-blind or open-label RCTs that compared favipiravir with placebo or another active pharmaceutical product at a therapeutic dose for the acute treatment of people of all ages with COVID-19 diagnosed using primary standard diagnostic criteria [23] (a positive real-time polymerase chain reaction (RT-PCR) test or typical ground glass appearance on chest CT scan). Furthermore, all traditional antiviral medications and other pharmaceuticals approved by pharmaceutical and medical device regulatory bodies in North America, Europe, and China were included and dietary supplements or botanical medications were excluded: Favipiravir, Tocilizumab, Favipiravir + Tocilizumab, Lopinavir + Ritonavir, Chloroquine, and Arbidol. Fixed-dose and variable-dose designs were also included. We offer detailed information on review procedures in Flow diagram 1.

We have determined the periods of one week to four months for outcome evaluations because we wished to look into the safety of favipiravir for acute therapy in the short term. We used data from the trial's time endpoint and included seven antivirals or placebo, clinical outcome indicators, and various impact modifiers. Our experiments rely on the most potent network meta-analysis statistical approach available. Journal articles, conference papers, sponsor publications, e.g., trial summaries, and documents from regulatory evaluations and filings were all evaluated for inclusion. Finally, we eliminated preliminary

randomized trials and ongoing projects. Hand searching for published and unpublished trials in clinical centers and relevant scientific publications in the region supplemented the automated database searches. Because patients with consistent symptoms and traits are essential for NMA [24], two investigators (K.Y and J.Z) independently searched the studies and detailed information and participant characteristics from the eligible RCTs with quantifiable estimates or precise data for ORs calculation. We assessed the risk of bias based on the Cochrane risk of bias (RoB) tool [25]. All included RCTs were reviewed by two independent researchers (W.D and M.C), who rated them as 'low risk,' 'high risk,' or 'unclear risk,' based on the following seven criteria: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Any disagreements were settled by the research team (K.Y, J.Z, W.D, M.C, and F.Y). This network meta-analysis provides a complete evidence base currently available to guide pharmacological treatment options for COVID-19 patients. The entire protocol for this NMA has been disclosed by INPLASY: INPLASY2021100099.

Outcome and statistical analysis

The primary outcomes of this study included the detection of adverse events (measured by the total number of patients in each group who experienced an adverse event). ORs were used to calculate effect sizes, and statistical significance was determined if the 95% confidence interval did not include 1 or if the *p* value was less than 0.05.

We conducted a Bayesian network meta-analysis with a random-effects model to synthesize data from studies that looked at many therapies (Favipiravir, Tocilizumab, Arbidol, Lopinavir + Ritonavir, Chloroquine, and control). A Bayesian method based on Makarov chain Monte Carlo simulation [26] was implemented using the free R package 'gemtc', we calculated each model by generating 10,000 adapt and 25,000 sample iterations; The model incorporates univariate random effects in assessing medium to considerable trial heterogeneity, and overall findings will be shown in a relative forest plot. Patients in the control group were given a placebo or the standard of care. The between-design inconsistency and within-design heterogeneity were also assessed using a design-based decomposition of Cochran's Q and I^2 statistical tests [27]. A ranking probability heat map was developed, analogous to the surface under the

cumulative ranking (SUCRA) value [28]. Here, a higher probability value indicates a more effective treatment. We also constructed an overall network diagram. The nodes in the network represent the myriad of therapies available. The thickness of the connecting lines reflects the number of studies that provide direct comparative results between the two therapies, and the size of the nodes is proportional to the number of patients involved in the treatment. We created a league table to visualize all direct and indirect comparisons, and the visual inspection of the Brooks–Gelman–Rubin diagnostic ensured model convergence [29]; the potential size reduction factor (PSRF) displayed in the curve in the image should eventually drop to 1 as the number of rounds increases. To assess the consistency of direct and indirect comparisons, we used the node splitting approach [30]. The research took place between October 12, 2021 and October 26, 2021, and the data analyses were conducted between October 26, 2021, and November 10, 2021.

Results

We searched PubMed ($n = 16$), medRxiv ($n = 185$), the Cochrane Library ($n = 115$), Clinical Trials ($n = 59$), and WHO ICTRP ($n = 90$), and ultimately selected 480 articles, 15 of which were hand-searched for other review papers. After removing duplicate data ($n = 448$), 32 potentially suitable articles and ineligible publications were identified by analyzing the titles and abstracts. Following a full-text review, 26 publications were omitted because of ongoing investigations, three studies were excluded due to the absence of published results, and six articles [15,31–35] were eventually included. Six open-label parallel RCTs (with a total of 908 individuals) were conducted between 2020 and 2021, evaluating seven antiviral medicines vs. placebo. The average study sample size was 151 individuals. 814 people were randomly assigned to active medications, whereas 94 were treated with a placebo. The overall mean age was 53.6 years, with 345 (37.99%) of the 908 people included being female. 94 (10.35%) of the 908 participants were randomized to placebo-controlled trials, and all six RCTs were multi-center research. 303 (33.37%) of the 908 recruited patients were from China, 148 (16.30%) from India, 84 (9.25%) from Egypt, and 373 (41.07%) from Iran. 73.12% of total patients were diagnosed with moderate-to-severe COVID-19, and the clinical signs were defined as pneumonia (fever, cough, dyspnoea, fast breathing) or pneumonia (fever, cough, dyspnoea) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or oxygen saturation (SpO_2) $< 90\%$ on room air. Pharmaceutical

corporations financed one research. The detailed characteristics of included studies are included in Table 1 and the antiviral treatment network plot is illustrated in Figure 1.

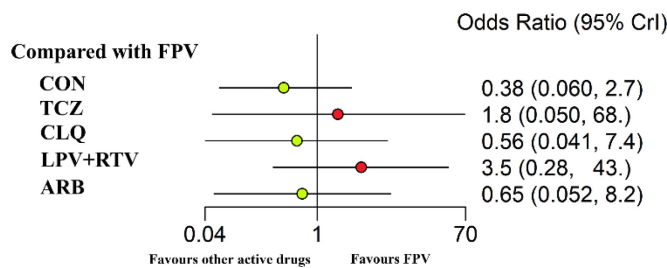
Risk of adverse events

We did not find evidence of a relationship between favipiravir treatment and adverse events [favipiravir versus control: OR = 0.38 (95% CI 0.06–2.70); tocilizumab versus favipiravir: OR = 1.80 (95% CI 0.05–68.00); chloroquine versus favipiravir: OR = 0.56 (95% CI 0.041–7.4); lopinavir + ritonavir versus favipiravir: OR = 3.50 (95% CI 0.28–43.00); arbidol versus favipiravir: OR = 6.50 (95% CI 0.052–8.20)] for small sample size and limited number of RCT as shown in Figure 2. We concluded that control treatment and chloroquine treatment tend to have the least adverse events with SUCRA values of 0.7676 and 0.6426, as shown in Figure 3. The league table of overall comparison is illustrated in Figure 4.

Quality assessment

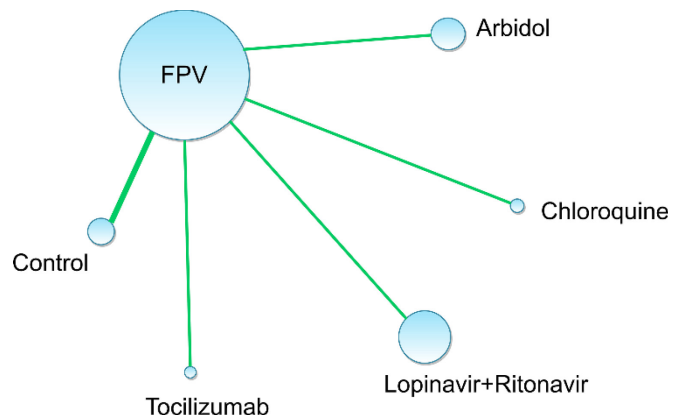
Because of the open-label design, all studies were classified as having a high risk of performance bias (blinding of participants and employees). Other items were scored as having a low risk of bias.

Figure 2. Forest plot of NMA results for safety events outcomes with favipiravir as reference compound, ORs more than 1 with red color favors favipiravir, ORs less than 1 with yellow color favors other active drugs.



FPV: favipiravir; CON: control; TCZ: tocilizumab; CLQ: chloroquine; LPV: lopinavir; RTV: ritonavir; ARB: arbidol; NMA: network meta-analysis; CrI: credibility interval.

Figure 1. Antiviral treatment network plot for hospitalized Covid-19 patients. The size of each navy-blue node represents the overall sample size. The width of each link represents the number of studies.



FPV: favipiravir.

Figure 3. Heat map graph of the ranking probability and SUCRA value. The ranking probability and SUCRA value were used to create a heat map graph of efficacy. A heat map graph is a color-coded graphical representation of data that shows the relative strength of each treatment. The red box represents a higher SUCRA value, indicating a higher likelihood of being the best treatment arm. In comparison, the white box represents a lower SUCRA value, indicating a lower probability of being the best treatment arm. Each box has a description of the values, which range from 0 to 1.

| | FPV | CON | TCZ | CLQ | LPV+RTV | ARB | value |
|---------------|--------|--------|--------|--------|---------|--------|-------|
| RANK 1 | 0.0083 | 0.382 | 0.1281 | 0.2597 | 0.0198 | 0.2018 | |
| RANK 2 | 0.0863 | 0.3025 | 0.1047 | 0.2404 | 0.0365 | 0.2293 | 1 |
| RANK 3 | 0.2914 | 0.1651 | 0.101 | 0.1835 | 0.0515 | 0.2072 | 0.75 |
| RANK 4 | 0.4146 | 0.087 | 0.1068 | 0.1427 | 0.084 | 0.1646 | 0.5 |
| RANK 5 | 0.1825 | 0.0481 | 0.2394 | 0.1166 | 0.2793 | 0.1337 | 0.25 |
| RANK 6 | 0.0166 | 0.015 | 0.3196 | 0.0568 | 0.5286 | 0.0631 | 0 |
| SUCRA | 0.4546 | 0.7676 | 0.3632 | 0.6426 | 0.1694 | 0.6022 | |

FPV: favipiravir; CON: control; TCZ: tocilizumab; CLQ: chloroquine; LPV: lopinavir; RTV: ritonavir; ARB: arbidol; SUCRA: the surface under the cumulative ranking.

Table 1. Characteristics of the eligible studies in this NMA.

| Trial | Location | Duration | Treatment (n) | Groups | Patient severity |
|--------------|----------|-------------|---|--------|-------------------------------------|
| Udwadia 2021 | India | One month | Favipiravir (73) / Control (75) | 2 | mild-to-moderate |
| Zhao 2021a | China | Two weeks | Favipiravir (7) / Tocilizumab(5) | 2 | adults with COVID-19 |
| Dodaran 2021 | Iran | One week | Favipiravir (190) / Lopinavir + Ritonavir (183) | 2 | moderate to severe |
| Zhao 2021b | China | One month | Favipiravir (36) / Control (19) | 2 | SARS-CoV-2 RNA re-positive patients |
| Dabbous 2021 | Egypt | Four months | Chloroquine (48) / Favipiravir (36) | 2 | mild or moderate |
| Chen 2020 | China | Two weeks | Favipiravir (116) / Arbidol (120) | 2 | moderate and severe |

Discussion

To the best of our knowledge, this is the first systematic study of the safety of favipiravir in the treatment of COVID-19 patients. Our network meta-analysis of six RCTs comprising 908 individuals investigated the safety of favipiravir in treating COVID-19 patients compared to the efficacy of other medications. We could not find a positive or negative effect of favipiravir medication on the safety of hospitalized COVID-19 patients because the number of RCTs and sample size were insufficient, and the difference was not statistically significant. Nonetheless, our meta-analysis includes the most recent RCT and a final report. Our findings are based on a survey of over 900 patients, providing more current information and more substantial evidence than past research.

Although a previous study found pervasive adverse effects, e.g., diarrhea, nausea, skin rash, and liver or kidney damage, this meta-analysis found no evidence of an increased risk of adverse events after favipiravir treatment compared to controls [36]. Our findings point out that favipiravir may be a safe antiviral medication for treating SARS-CoV-2 infection.

According to a recent review article, the primary mechanism by which favipiravir hampers the COVID-19 virus is through inhibition of RNA-dependent RNA polymerase. As an oral drug, its standard dose to treat influenza is 1600 mg twice daily on the first day, followed by 600 mg twice daily for five days. This dosage promotes significant clinical improvements, including respiratory rate, cough relief of cough and improvement in chest CT, and has a tolerable safety profile for overall and serious adverse effects compared to placebo [18]. Individuals using favipiravir had a higher frequency of grade 1 adverse effects such as thrombocytopenia, anaphylaxis, increased serum uric acid, and neurological [37]. According to the study by Zhao *et al.* [32], patients in the control group, on the other hand, experienced more significant side responses. In most studies, adverse reactions were considered mild or moderate in severity except for the worsening of primary viral infections. The severe course of COVID-19 is related to respiratory failure and pulmonary embolism. In a recent meta-analysis, except for the prevalence of rash (which was more significant in the favipiravir group), safety was equivalent to the SOC (standard of care) group [38]. Another meta-analysis published in May 2021 discussed the safety association between favipiravir treatment and different control groups and the results demonstrated a lower risk of side effects in the favipiravir arm, although this was not statistically significant (RR = 0.77, 95% CI: 0.34–

Figure 4. League table of anti-viral drugs’ safety comparisons based on the responder rates in the left grey triangle and their corresponding treatments in the upper cells. Comparisons between treatments should be read from left to right, with log odds ratios (ORs) less than 0 representing better results for the treatment option corresponding to the top of the estimates.

| | | | | | |
|------------------------|------------------------|------------------------|------------------------|-----------------------|-----|
| FPV | | | | | |
| 0.96 (-0.98, 2.81) | CON | | | | |
| -0.59 (-4.22, 3.00) | -1.54 (-5.57, 2.51) | TCZ | | | |
| 0.58 (-2.01, 3.20) | -0.38 (-3.54, 2.89) | 1.16 (-3.20, 5.62) | CLQ | | |
| -1.26 (-3.75, 1.26) | -2.24 (-5.29, 0.98) | -0.68 (-5.02, 3.73) | -1.85 (-5.45, 1.80) | LPV+RTV | |
| 0.43 (-2.10, 2.96) | -0.54 (-3.65, 2.65) | 1.01 (-3.39, 5.42) | -0.15 (-3.79, 3.44) | 1.69 (-1.90, 5.22) | ARB |

1.70; $p = 0.524$); however, we believe it would be more appropriate to use a network meta-analysis when considering different treatments in groups, and the original study appears to have resulted in some confirmed heterogeneity [39]. After favipiravir treatment, there were no major life-threatening side effects. As patients received other medicines in some trials, possible side effects could not be ascribed only to the use of favipiravir. In addition, due to the risk of teratogenicity and embryotoxicity associated with this chemical [40], the treatment of pregnant women and children requires more caution. It has also been suggested that blood favipiravir levels may be negatively correlated with blood ferritin levels in the treatment of patients with moderate to severe COVID-19 [41], and a clinical study has shown that favipiravir is ineffective in patients with elevated ferritin and that patients with high blood favipiravir levels frequently have elevated uric acid levels [42], implying that monitoring blood favipiravir levels is especially important when treating patients with COVID-19.

It is equally important to acknowledge the limitations of our research. Our sample size and number of studies considered are minimal, resulting in statistically inconsequential conclusions. As a result, we must be vigilant when forming conclusions. Because of the small number of trials, we could not determine the heterogeneity of overall outcomes due to changes in baseline severity and definitions of recovery and improvement in patients diagnosed with COVID-19. Another unresolvable distinction was the variation in recruitment age between the trials, with one [32] that only focused on participants that were 70 years or older and the other [31,33–35] including participants from 30 to 50 years. Because the current meta-analysis cannot objectively confirm or invalidate these findings, the results of a few studies should be interpreted with care.

Additionally, we did not undertake sensitivity analysis detection because of the small number of studies. Because all experiments were open-label with no blinding owing to ethical reasons, the interpretation of the data with a high evidence level may be hampered. The length of therapy and dose varied between studies in the qualitative analysis. RCTs in our study had different treatment durations. As mechanical ventilation (non-invasive or invasive) is another critical factor in managing COVID-19, low-dose therapy is considered a poor prognostic factor for clinical improvement in COVID-19. It is crucial to determine the appropriate dose and duration of favipiravir therapy from a drug metabolism perspective, considering that the duration of treatment in the studies we included in our analysis varied and that hospitalized critically ill patients often lacked effective plasma concentrations [43].

Conclusions

The network meta-analysis results of this study imply that favipiravir may increase adverse events compared to placebo, but not when compared to other antivirals. Favipiravir is distinguished by its significant COVID-19 virus inhibition and lack of viral resistance, but more in-depth research on the safety of this drug is needed in the future.

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Authors' Contributions

Kai Yang was in charge of the search, quality evaluation, data analysis, and paper authoring. Jun Zeng, Wenjing Dai, and Meifeng Chen carried out study research, quality evaluation, and data extraction. Jun Zeng assisted in the search for and selection of papers and the main structuring of the paper. Fan Yang was in charge of the final revision after revising each phase of the work.

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Conflict of interests: No conflict of interests is declared.

Annex – Supplementary Items

Supplementary Table 1. Electronic search strategy.

| Database | Queries |
|---|--|
| PubMed | (((((("coronavirus"[Mesh] OR "corona virus"[Mesh] OR "corona"[Mesh] OR "2019-nCoV"[Mesh] OR "COVID-19"[Mesh] OR "Covid19"[Mesh] OR "SARS-CoV"[Mesh] OR "SARSCov2"[Mesh])) AND ("favipiravir"[Mesh] OR "avigan"[Mesh]))) AND ((randomized controlled trial [pt] OR (randomized [tiab] AND controlled [tiab] AND trial [tiab] AND RCT [tiab])) NOT ((animals [mh] NOT review[ti]) OR (review [pt] OR meta-analysis [pt])))) |
| Cochrane Central Register of Controlled Trials | <ol style="list-style-type: none"> 1. MeSH descriptor: [coronavirus] explode all trees 2. MeSH descriptor: [COVID-19] explode all trees 3. corona virus or corona or 2019-nCoV or Covid19 or SARS-CoV:ti,ab,kw 4. #1 OR #2 OR #3 5. MeSH descriptor: [favipiravir] explode all trees 6. MeSH descriptor: [avigan] explode all trees 7. #5 OR #6 8. MeSH descriptor: [randomized controlled trial] explode all trees 9. MeSH descriptor: [trial] explode all trees 10. MeSH descriptor: [RCT] explode all trees 11. MeSH descriptor: [clinical trial] explode all trees 12. #8 OR #9 OR #10 OR #11 13. #4 AND #7 AND #12 |
| Clinical Trials. gov | Status: All studies Condition or disease: COVID-19 Other terms: favipiravir |
| International Clinical Trials Registry Platform | Favipiravir |
| medRxiv | Favipiravir |

Supplementary Table 2. PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis.

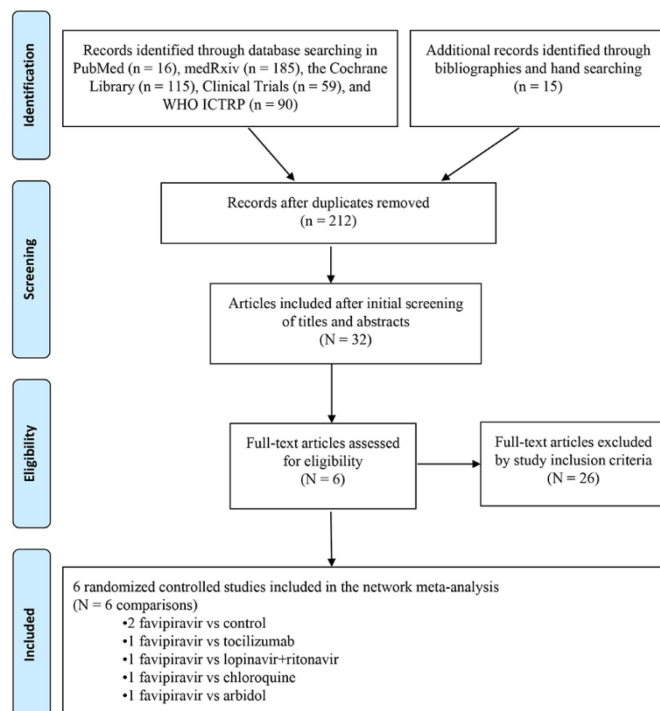
| Section/Topic | Item # | Checklist Item | Reported on Page # |
|---------------------------|--------|---|--------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> . | 1 in full text |
| ABSTRACT | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: Primary source of funding; systematic review registration number with registry name. | 2 in full text |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted.</i> | 3 in full text |
| Objectives | 4 | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3 in full text |
| METHODS | | | |
| Protocol and registration | 5 | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number. | 4 in full text |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same</i> | 3, 4 in full text |

| | | | |
|--|-----------|--|--|
| | | <i>node (with justification).</i> | |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3 in full text |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 3, 4 in full text |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 4 in full text |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3, 4 in full text |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4 in full text |
| Geometry of the network | S1 | Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers. | 4 in full text |
| Risk of bias within individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 4 in full text |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i> | 4 in full text |
| Planned methods of analysis | 14 | Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> | 4 in full text |
| Assessment of Inconsistency | S2 | Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found. | 4 in full text |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 4 in full text |
| Additional analyses | 16 | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> | 4 in full text |
| RESULTS† | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 4, 5 in full text; 3 in supplementary |
| Presentation of network structure | S3 | Provide a network graph of the included studies to enable visualization of the geometry of the treatment network. | 6 in full text |
| Summary of network geometry | S4 | Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure. | 5, 6 in full text |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 5 in full text |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment. | 8 in full text |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i> | 6 in full text |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.</i> | 6 in full text |

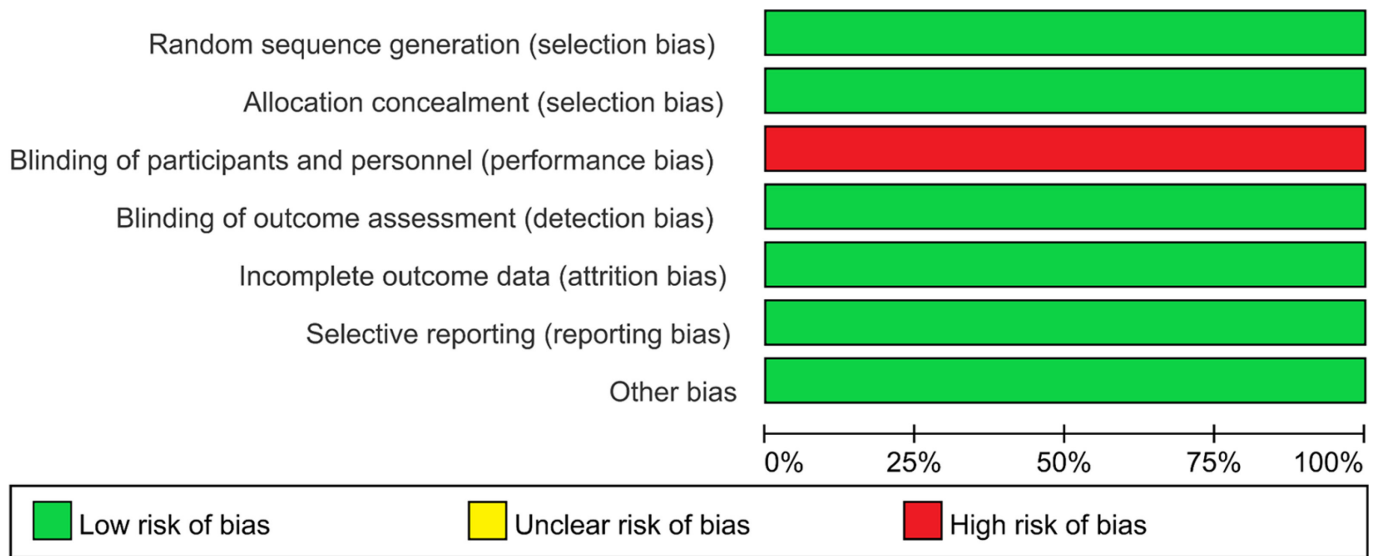
| | | | |
|--------------------------------------|----|--|------------------------------------|
| Exploration for inconsistency | S5 | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network. | 6, 7, 8, 9, 13 in supplementary |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies for the evidence base being studied. | 8 in full text; 4 in supplementary |
| Results of additional analyses | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>). | 10, 11, 12 in supplementary |
| DISCUSSION | | | |
| Summary of evidence | 24 | Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers). | 8 in full text |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons)</i> . | 9 in full text |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9 in full text |
| FUNDING | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network. | |

PICOS: population, intervention, comparators, outcomes, study design. * Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement. † Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplementary Figure 1. Flow diagram.



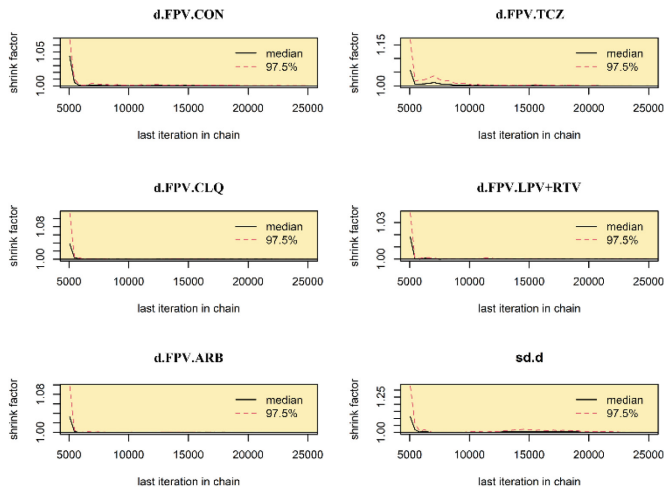
Supplementary Figure 2. “Risk of bias” graph.



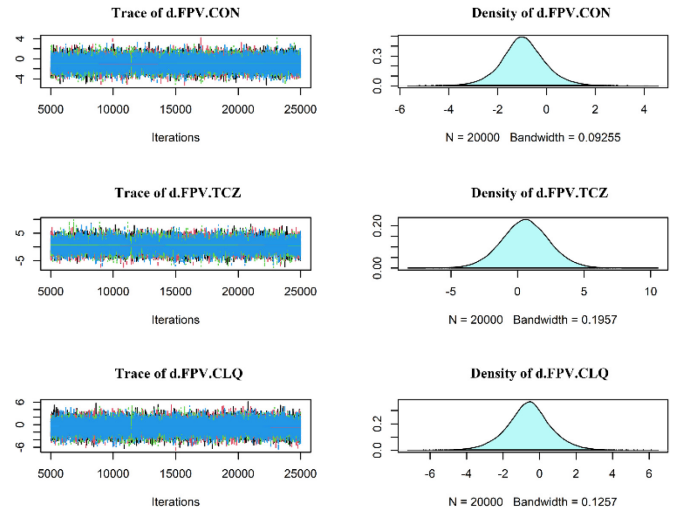
Supplementary Figure 3. “Risk of bias” summary.

| | 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 |
|--------------|---|---|---|---|--|--------------------------------------|------------|
| Chen 2020 | + | + | - | + | + | + | + |
| Dabbous 2021 | + | + | - | + | + | + | + |
| Dodaran 2021 | + | + | - | + | + | + | + |
| Udwadia 2021 | + | + | - | + | + | + | + |
| Zhao 2021a | + | + | - | + | + | + | + |
| Zhao 2021b | + | + | - | + | + | + | + |

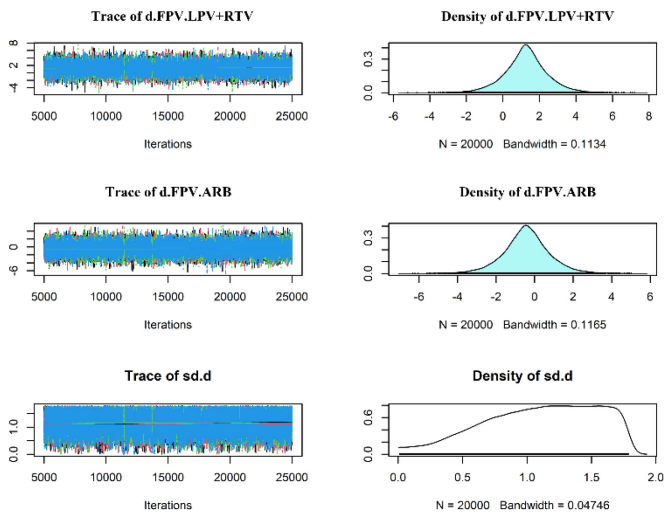
Supplementary Figure 4. The potential scale reduction factor (PSRF) of the Brooks–Gelman–Rubin method was used to determine model convergence in random effects model; PSRF closer to 1 indicated greater convergence.



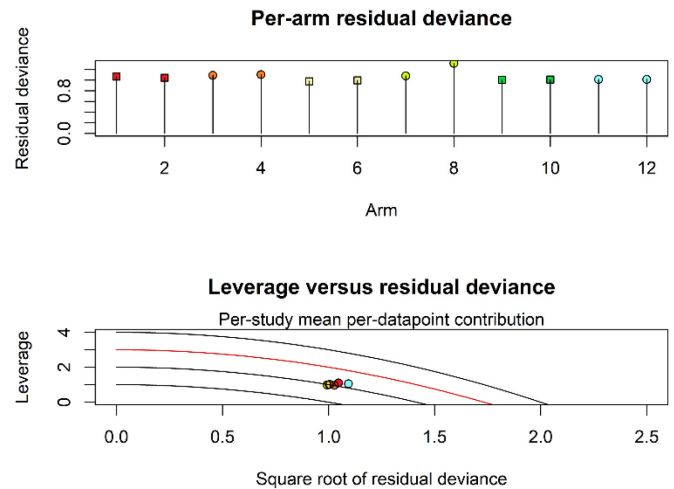
Supplementary Figure 5. The trace plot of each treatment comparison over all iterations to evaluate if there is considerably faster up-and-down volatility in random effects model.



Supplementary Figure 6. The trace plot of each treatment comparison over all iterations to evaluate if there is considerably faster up-and-down volatility in random effects model.



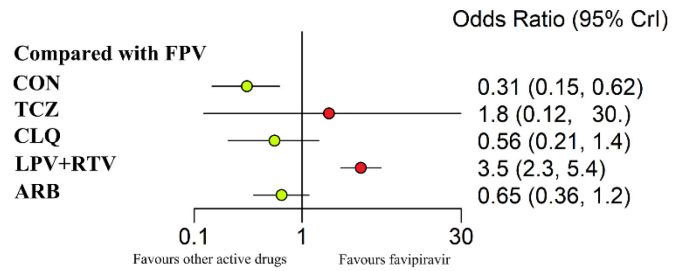
Supplementary Figure 7. Plot of leverage versus Bayesian deviance residual w_{ik} for each data point in random effects model, demonstrated that the majority of values that fall inside the sketched smooth parabola with a constant of 3.



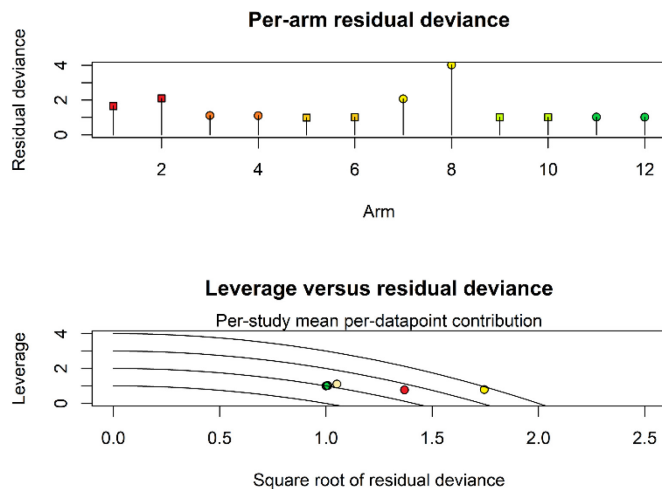
Supplementary Figure 8. The ranking probability and SUCRA value in fixed effect model were used to create a heat map graph of efficacy.

| | FPV | CON | TCZ | CLQ | LPV+RTV | ARB | value |
|--------|--------|--------|--------|--------|---------|--------|-------|
| RANK 1 | 0 | 0.7284 | 0.0943 | 0.1447 | 0 | 0.0324 | |
| RANK 2 | 0.0052 | 0.2217 | 0.0802 | 0.3887 | 0 | 0.3041 | 1 |
| RANK 3 | 0.1142 | 0.0449 | 0.0805 | 0.2901 | 0 | 0.4701 | 0.75 |
| RANK 4 | 0.6076 | 0.0048 | 0.0853 | 0.1334 | 0 | 0.1687 | 0.5 |
| RANK 5 | 0.2728 | 0.0001 | 0.3488 | 0.0429 | 0.3107 | 0.0245 | 0.25 |
| RANK 6 | 0 | 0 | 0.3107 | 0.0001 | 0.6891 | 0 | 0 |
| SUCRA | 0.3703 | 0.9347 | 0.3107 | 0.6917 | 0.0621 | 0.6302 | |

Supplementary Figure 9. Forest plots of NWM results for safety events outcomes with favipiravir as reference compound in fixed effect model, ORs more than 1 with red color favour favipiravir, ORs lower than 1 with yellow color favour other active drugs.



Supplementary Figure 10. Plot of leverage versus Bayesian deviance residual for each data point in fixed effects model, demonstrated that the majority of values that fall inside the sketched smooth parabola with a constant of 3.



Supplementary Figure 11. Qualitative and quantitative testing for publication bias in NMA.

