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Research Article

Role of Favipiravir therapy in COVID 19 patients A Systematic Review and Meta Analysis

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Abstract: The ongoing global problem of concern is the Coronavirus Disease 2019 (COVID-19) caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). With the sudden explosion of the disease, no drugs were experimentally proven in its management. This meta-analysis assessed the role of favipiravir in the management of COVID 19 disease, its efficacy and safety. A comprehensive search of databases including PubMed, Medline, Cochrane, Embase, Google scholar, Lancet, Elsevier and other modalities of search like website searching and citation tracking was made. Out of 687 articles identified, 8 articles were taken for the meta-analysis after several stages of exclusion. Out of the 8 studies selected, the results of 4 studies were in favour of favipiravir, while other 4 studies were against the efficacy of favipiravir. The result of our statistical analysis was that RR=0.9276 (95% CI; 0.6718 to 1.3944) for the effect of favipiravir on mortality reduction in COVID 19 patients. Favipiravir treatment in the early phase of infection (viral replication phase) have shown significant reduction in the viral load and good clinical recovery. It also prevents the progression of disease to critical stage by controlling the infection adequately in the early phase itself. But when the stage of viral replication has passed, there is no role of favipiravir in the management of the COVID 19 disease. Favipiravir has no significant effect on mortality reduction in COVID 19 patients.

Keywords: Antivirals, COVID 19, Favipiravir, Pharmacotherapy, Repurposing drugs, SARS CoV 2.

INTRODUCTION

The ongoing global problem of concern is the Coronavirus Disease 2019 (COVID-19) caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 disease manifests grossly in 2 phases: The early phase of mild illness is caused by the virus followed by a late phase of severe and critical illness which is solely constituted by dysregulated inflammatory and immune responses (Srikumar, S., & Perumal, S. 2021). It is crucial to understand the course of the disease while aiming for treatment, as the treatment modality varies with the various stages. Early intervention, when possible, should predominantly target the viral multiplication that can largely limit the progression of the disease and the aftermath (Furuta, Y. *et al.*, 2017).

With the compelling need to discover therapeutic options for COVID-19 disease, the idea of repurposing the existing drugs were thought (Lee, J. S. *et al.*, 2019). Favipiravir, a purine nucleic acid analogue was initially developed by Toyama Chemical Co., Ltd. in Japan for the treatment of mild viral infections (FUJIFILM Toyama Chemical Co., Ltd.). It acts by inhibiting RNA dependent RNA polymerase enzyme (RdRp), thereby hindering the multiplication of RNA viruses (Manabe, T. *et al.*, 2021). Ever since the COVID-19 disease was reported a pandemic, the role of favipiravir against SARS-CoV-2 was being evaluated. Various studies on favipiravir conducted during this crisis have shown mixed results: some regard it as a promising choice while others regard it as not of much significance. The intent of this meta-analysis is to assess the role of favipiravir, it's safety and efficacy in the treatment of COVID-19.

MATERIALS AND METHODS

This systematic review was performed in strict accordance with the Preferred Reporting Items of the Systematic review and Meta-Analysis (PRISMA) checklist. All steps were compliant with the Cochrane Handbook of Systematic Review and Meta-Analysis.

Search Strategy

We conducted a comprehensive literature review by searching the databases like PubMed, Medline, Cochrane, Embase, Google scholar, Lancet, Elsevier. The following search terms were used: 'Favipiravir' 'Drug trials' 'Pharmacotherapy' 'randomized control trials' 'antivirals'. The search also included mining references from good quality articles, website searching and citation tracking.

Inclusion criteria

- Studies on COVID-19 conducted between April 2020 and July 2021
- Studies on pharmacotherapy for COVID-19 specially focussing favipiravir
- Studies with sample size >100
- Studies with good methodologies
- Studies with properly outlined efficacy and safety endpoints of favipiravir

Exclusion criteria

- Articles on COVID published before 2020
- Studies showing in-vitro effects of favipiravir
- Abstract-only papers, articles with full texts not available
- Articles with only guidelines/protocol for management of COVID 19
- Articles published in languages other than English

Data Extraction

The data was extracted independently from the eligible studies. The reliability of the data was cross-checked by reviewing the same article in multiple other systematic reviews of various authors. Generic inverse variance method (random-effects model) was used to estimate the odds ratios (OR) of patients for primary outcome variables with 95% confidence intervals (CI). Results after adjustments and propensity score matching were taken to eliminate 'Selection bias'.

Statistical analysis

The odds ratios with 95% confidence intervals of the individual studies were compiled. The data were processed using the Statistical Package for the Social Sciences (SPSS) software version 20.0.

RESULTS

Study selection

A total of 687 articles were identified via database searches, website searching and reference chaining. After eliminating duplicate studies (143), articles that were inappropriate to the study topic (227) and articles that did not fit the eligibility criteria (303), 14 articles were eligible. After quality assessment, 8 articles were taken for the meta-analysis, of which 5 were Randomized control trials and 3 were Observational studies (Fig.1).

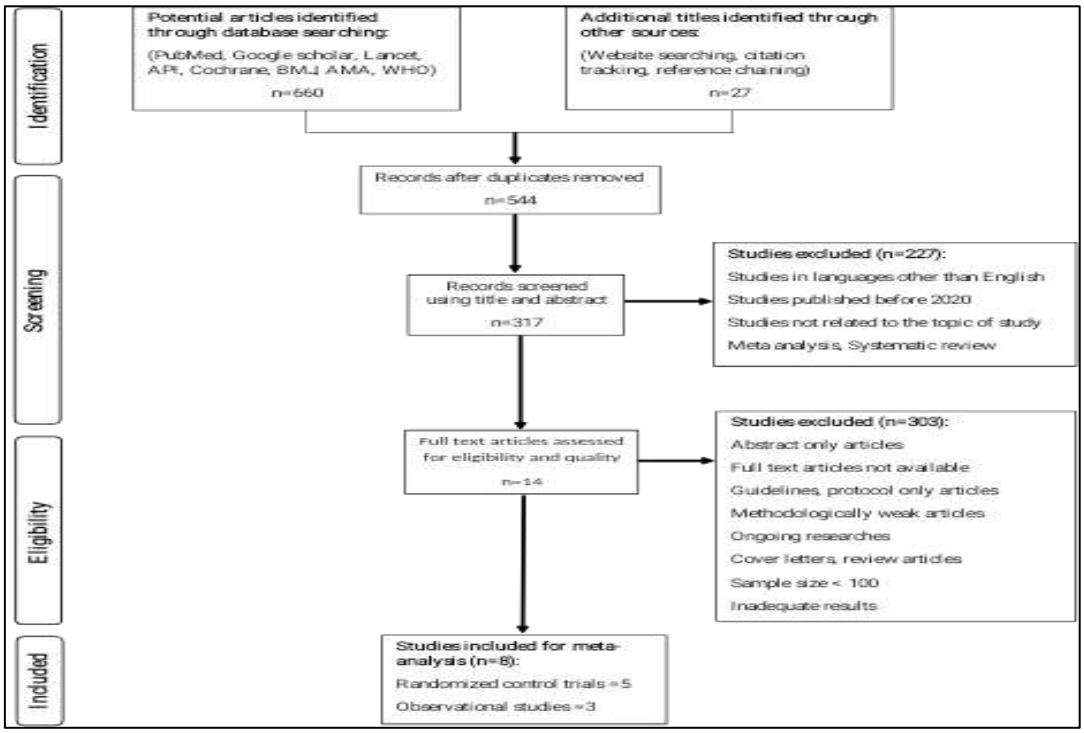

Fig.1: Prisma flow chart showing study selection

Study characteristics

The studies were chosen based on the following details: date of publication, study design, country where the study was conducted, sample size, number of patients in the intervention group - treated with favipiravir, combination of drugs if given, number of deaths, number of ICU admissions, invasive mechanical ventilation, viral clearance time, length of hospital stay,

comorbidities and number of patients in the control group who received standard care of treatment/placebo.

Synthesis of Results

In our meta-analysis, the following parameters were evaluated:

a) Time taken for clinical recovery
b) Length of hospital stay
c) Changes in SpO2 levels during hospitalization
d) Mortality

Data of 4304 patients collected from 8 studies conducted in different parts of the world are shown in Table 1.

Table 1: Summary of studies analysed in the meta-analysis

S. No	Study ID	Country	Study design	Sample Size	Experimental group	Comparative group	Results	Description
1.	Masoud *et al.,* (2021)	Iran	Multicentre observational study	380	Patients treated with favipiravir (193)	Patients treated with lopinavir/ ritonavir (187)	HR=0.94 for clinical recovery in patients taking favipiravir vs lopinavir/ ritonavir.	Hospital stay and the time to clinical recovery of patients with favipiravir did not vary when compared to lopinavir and ritonavir.
2.	Yohei Doi *et al.,* (2020)	Japan	Observational study	2158	-	-	Rates of symptomatic improvement were 87.8%, 84.5% and 60.3% at 14 days for mild, moderate and severe disease, respectively.	Majority of patients who had taken favipiravir have had significant improvement and recovery of illness.
3.	Corritori *et al.,* (2021)	Russia	RCT	940	Patients who took favipiravir (470)	Patients on standard care (470)	Median time of viral clearance in favipiravir group and standard care are 6 and 12 days, respectively.	Favipiravir has a high clinical efficacy and tolerability in covid 19 patients.
4.	Pinyo Rattanaumpawan *et al.,* (2020)	Thailand	Multicentre observational study	247	Patients who received Favipiravir (63)	Patients who did not receive Favipiravir (184)	The clinical improvement rate on day 7 was 66.7% in all patients, 92.5% in patients who did not require O2-supplementation, and 47.2% in patients who required O2-supplementation.	Favipiravir shows promising effects in Covid-19.
5.	Chang Chen *et al.,* (2020)	China	Prospective, open-label multicenter RCT	240	Patients who received Favipiravir (120)	Patients who received arbidol (120)	On day 7, the clinical recovery rate did not significantly vary between Favipiravir group (71/116) and Arbidol group (62/120).	Favipiravir did not significantly improve clinical recovery rate when compared with arbidol.
6.	Zarir F. Udwadia *et al.,* (2020)	India	Open-label, parallel-arm, multicenter RCT	150	Patients treated with favipiravir (75)	Patients not treated with favipiravir (75)	Median time to clinical improvement of symptoms was 3 days in the favipiravir group vs 5 days in the control group.	In mild to moderate COVID 19 patients, use of favipiravir showed significant clinical improvement in 3

								days.
7.	Faryal Khamis *et al.*, (2020)	Oman	Open-label RCT	89	Patients who received Favipiravir + inhaled interferon beta-1b (44)	Patients who received HCQ (45)	The mortality rates were 11.4% and 13.3% in patients who received Favipiravir + inhaled interferon beta-1b and HCQ, respectively.	There was no significant reduction in mortality among hospitalised patients who received Favipiravir and inhaled interferon beta-1b combination therapy.
8.	Hany M. Dabbous *et al.*, (2021)	Egypt	RCT	100	Patients treated with favipiravir (50)	Patients treated with HCQ + Oseltamivir (50)	PCR seronegative conversion on day 7 was 48% and 55.1% in the favipiravir and HCQ + oseltamivir groups, respectively.	In mild to moderate COVID 19 patients, treatment with favipiravir showed similar effects to that of HCQ and oseltamivir combination therapy.

Out of the 8 studies selected, the results of 4 studies were in favour of the use of favipiravir, while other 4 studies were against the efficacy of favipiravir. The result of our statistical analysis was that the relative risk (Fig.2) for mortality reduction of favipiravir in COVID 19 patients is 0.9276 (95% CI; 0.6718 to 1.3944).

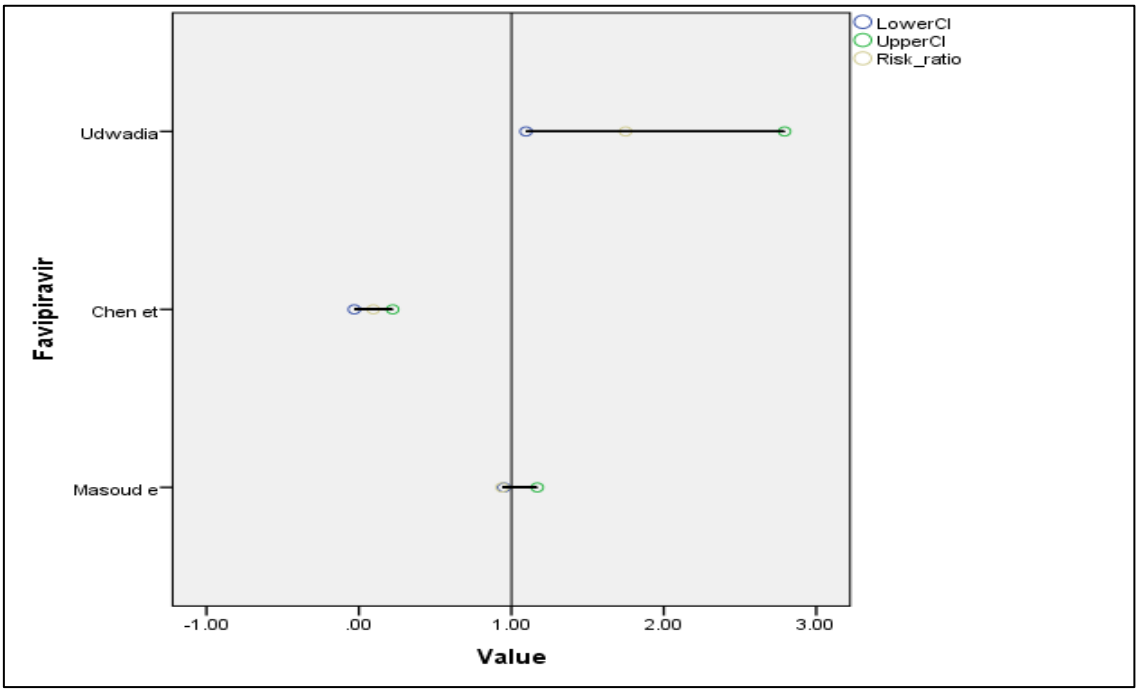

Fig.2: Relative risk of mortality reduction of favipiravir as per the analysed studies

Risk of bias assessment

We assessed the risk of bias ('low risk', 'unclear', or 'high risk') for the studies included in the meta-analysis using version 2 of the Cochrane Risk of Bias assessment tool for randomised control trials (Fig.3) and The New Castle Ottawa scale for non-randomised controlled trials (Table 2). Disagreements aroused during this process were resolved through discussion. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was utilised to assess the quality of the evidence obtained from various studies.

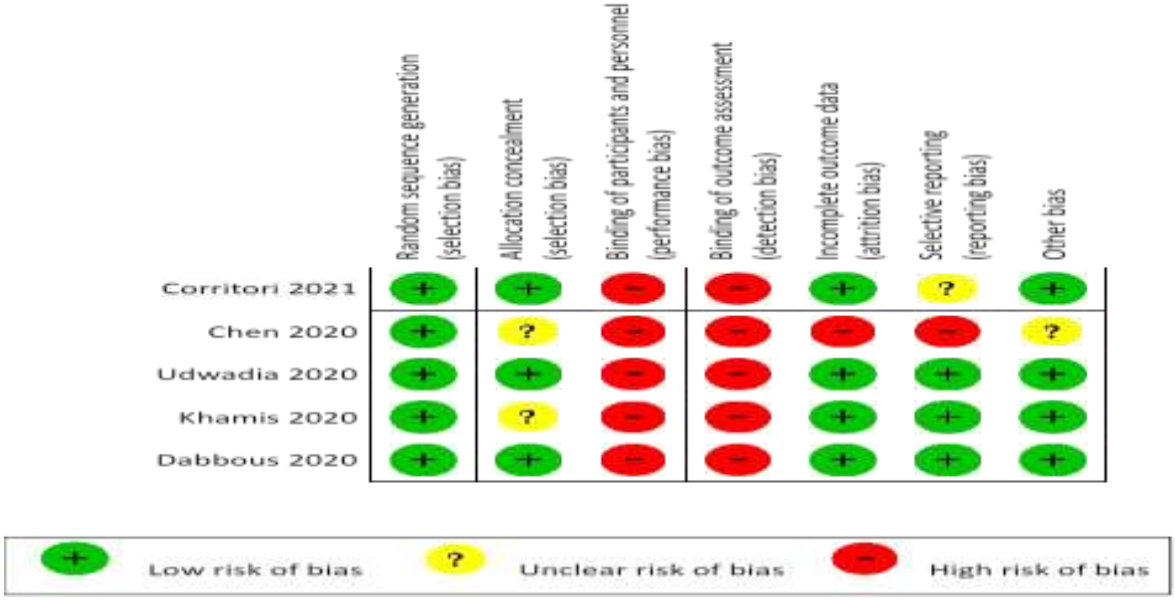

Fig. 3: The Cochrane Risk of bias assessment for randomised control trial studies analysed

Table 2: The New Castle Ottawa scale for non-randomised controlled trial studies analysed

Study ID	Selection			Comparability*	Outcome		Total (7★)
	Representativeness of exposed cohort (★)	Selection of non-exposed cohort (★)	Ascertainment of exposure (★)	(★★)	Assessment of outcome (★)	Adequacy of follow up (★)	
Masoud 2021	★	★	★	★★	-	-	★★★★★★ (6)
Doi 2020	-	-	-	★ -	★	★	★★★ (3)
Rattanaumpawan 2020	★	-	-	★★	★	-	★★★★ (4)

DISCUSSION

SARS CoV-2 is a single stranded positive sense RNA virus belonging to the corona viridae family. It is an enveloped virus with spike proteins on its surface (Zumla, A. *et al.*, 2016). The virus encodes proteases and the enzyme RNA-dependent RNA polymerase (RdRp) (Vora, A., & Tiwaskar, M. 2020). Both RdRp and viral proteases were considered as prime targets for the development of potential therapeutic agents. Favipiravir is one such attempt.

Previously known as T-705, favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamid) is a pro-drug. Intracellularly, it undergoes ribosylation and phosphorylation to form favipiravir ribofuranosyl-5′-triphosphate (Favipiravir- RTP), the active metabolite. Favipiravir-RTP competes with purine nucleosides and hinders the viral replication. It integrates with the nascent viral RNA causing inhibition of viral RdRp which leads to termination of the chain and viral mutations (Shannon A, *et al.*, 2020). Oral favipiravir is well absorbed with bioavailability of nearly 97.6%. Like most of the drugs, favipiravir is metabolized in liver, mostly by Aldehyde Oxidase enzyme and partly it is converted to a hydroxylated form by the enzyme Xanthine Oxidase. The hydroxylated form is then excreted by the kidneys (Du YX, *et al.*, 2020; & AVIGAN 2017).

Time taken for clinical recovery

In an observational study of 380 patients conducted by Masoud *et al.*, in Iran, treatment with favipiravir showed no difference in the time taken for clinical recovery when compared to the control group. The hazard ratio calculated using Cox proportional hazard modelling was 0.94 (95% CI: 0.75-1.17) (Solaymani-Dodaran, M. *et al.*, 2021). The results were similar to that of the RCT conducted by Chang Chen *et al.*, in China with 240 patients. The difference of recovery rate was 0.0954 (95% CI: 0.0305-0.2213) between the favipiravir group and the arbidol (control) group (Chen,

C. *et al.,* 2021). Further studies by Yohei Doi *et al.,* in Japan involving 2158 patients (Doi, Y. *et al.,* 2020) and by Pinyo Rattanaumpawan *et al.,* in Thailand involving 247 patients (Rattanaumpawan, P. *et al.,* 2020) also showed results that were consistent that time taken for clinical recovery in patients taking favipiravir and that of the control group was almost alike.

Length of stay in hospital

When observed the medically discharged patients as per physician's advice in Masoud *et al.,* study (Solaymani-Dodaran, M. *et al.,* 2021), the median length of hospital stay was 7 days in the favipiravir group and 6 days in the control group (p=0.85). There was no significant variation between the results of the two groups. This is supported by the Randomised controlled trial conducted on 89 patients by Faryal Khamis *et al.,* at Oman (Khamis, F. *et al.,* 2021). The length of stay in hospital was similar in the favipiravir and the control group (p=0.948).

SpO2 change over-hospitalization

In the observational study by Masoud *et al.,* (2021), out of 380 patients taken in the study, 193 patients were on favipiravir and 187 were on lopinavir/ ritonavir. Supplemental oxygen was paused for 5 minutes in un-intubated patients among the two groups to look for changes in the oxygen saturation (SpO2). The results were indistinguishable (OR=1.00, 95% CI: 0.71–1.42; p = 0.997).

Mortality

In the Randomised controlled trial on 89 patients conducted by Faryal Khamis *et al.,* in Oman (Khamis, F. *et al.,* 2021), the mortality rates were 11.4% and 13.3% in the favipiravir and the non-favipiravir group (p=0.778). The results did not significantly differ among the two groups. It is in accordance to the results of Masoud *et al.,* study (Masoud *et al.,* 2021), where the number of deaths were 26 in the favipiravir group and 21 in the Lopinavir/Ritonavir group among the 47 deaths (p=0.49).

The possible explanation that could be regarded for the negative findings on the efficacy of Favipiravir against COVID 19 disease could be explained by the pathogenesis of this disease. The disease course includes 2 phases: The early phase of infection usually occurs in first 1 week from the day of acquiring the virus. Patients experience mild symptoms or are mostly asymptomatic (Catanzaro, M. *et al.,* 2020; & Siddiqi, H. K., & Mehra, M. R. 2020). When infection not controlled in the early phase due to factors like immunosuppressed state, immunocompromised patients, patients with comorbidities like diabetes, coronary artery disease, the patients progress to the later stage of the disease, which is constituted by a surge of inflammatory reactions in response to the uncontrolled viral load. This gush of immune and inflammatory mediators is called the 'cytokine shower' and when it is massive, it is called the 'cytokine storm (Wu, J. *et al.,* 2020; Mason, R. J. 2020; & Giammaria, D., & Pajewski, A. 2020)'. Therefore, treatment in the early phase should aim the viral replication and in late phase should target the cytokine storm. If the patients included in the above studies had passed the viral replication phase, they are unlikely to benefit from the antiviral treatment.

Adverse events

Favipiravir is a drug with well-established safety profile and is usually tolerated well. The frequently reported adverse effects were diarrhoea, increased serum uric acid level, reduction of neutrophil count and abnormal liver function tests showing raised transaminases (AST, ALT) (Fabiflu® 2020). On further evaluation of patients who had increased serum uric acid level, it was found that they had developed Acute kidney injury (AKI). They were non-oliguric; urine analysis was unremarkable and ultrasound showed features of neither obstructive uropathy nor renal vasculature thrombosis. The AKI improved within 24-48 hours of discontinuation of favipiravir treatment, eliciting the association with the drug. The respiratory failure of the patients had resolved and inflammatory markers were lowered which eliminates the possibility of direct SARS-CoV-2 related AKI. This suggests that the AKI caused was 'drug induced nephrotoxicity (Nasa, P. *et al.,* 2014)'.

Favipiravir causing teratogenicity and early embryonic lethality have been observed in several animal models. Therefore, premenopausal women should be cautioned and pregnancy must be excluded before initiating favipiravir treatment. It is also essential that all patients and their sexual partners practice safe contraception during the treatment course and till 10 days after the end of favipiravir therapy.

Limitations

Our study had two limitations. One, not all studies were Randomised controlled trials, which increases the risk of bias. Two, only 8 studies were taken for the review as no other studies were qualitatively and quantitatively eligible to take up. Many randomized controlled trials with ample sample size, reliable data collection and good quality results are necessary to arrive at more beneficial outcomes.

CONCLUSION

Favipiravir treatment in the early phase of infection (viral replication phase) have shown significant reduction in the viral load and good clinical recovery. It also prevents the progression of disease to critical stage by controlling the infection adequately in the early phase itself. But when the stage of viral replication has passed, there is no role of favipiravir in the management of the COVID 19 disease. Favipiravir has no significant effect on mortality reduction in COVID 19 patients.

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