European Journal of Clinical Microbiology & Infectious Diseases (2021) 40:2575–2583
https://doi.org/10.1007/s10096-021-04307-1

ORIGINAL ARTICLE

Effectiveness of favipiravir in COVID-19: a live systematic review

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Received: 1 March 2021 / Accepted: 5 July 2021 / Published online: 4 August 2021

Abstract

We performed a systematic review and meta-analysis for the effectiveness of Favipiravir on the fatality and the requirement of mechanical ventilation for the treatment of moderate to severe COVID-19 patients. We searched available literature and reported it by using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Until June 1, 2021, we searched PubMed, bioRxiv, medRxiv, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar by using the keywords "Favipiravir" and terms synonymous with COVID-19. Studies for Favipiravir treatment compared to standard of care among moderate and severe COVID-19 patients were included. Risk of bias assessment was performed using Revised Cochrane risk of bias tool for randomized trials (RoB 2) and ROBINS-I assessment tool for non-randomized studies. We defined the outcome measures as fatality and requirement for mechanical ventilation. A total of 2702 studies were identified and 12 clinical trials with 1636 patients were analyzed. Nine out of 12 studies were randomized controlled trials. Among the randomized studies, one study has low risk of bias, six studies have moderate risk of bias, and 2 studies have high risk of bias. Observational studies were identified as having moderate risk of bias and non-randomized study was found to have serious risk of bias. Our meta-analysis did not reveal any significant difference between the intervention and the comparator on fatality rate (OR 1.11, 95% CI 0.64–1.94) and mechanical ventilation requirement (OR 0.50, 95% CI 0.13–1.95). There is no significant difference in fatality rate and mechanical ventilation requirement between Favipiravir treatment and the standard of care in moderate and severe COVID-19 patients.

Keywords Favipiravir · COVID-19 · Effectiveness · Meta-analysis · Systematic review

Introduction

SARS-CoV-2 with an extremely high spreading potential caused a global crisis with significant bottleneck in diagnosis, treatment, and prevention. Despite the active search for an effective and definitive cure, there is no specific antiviral drug identified for the treatment of COVID-19 yet; this has been one of the most challenging aspects of the pandemic. Repurposing of existing antiviral agents against COVID-19 became the common approach to treatment [1].

Favipiravir, one of these repurposed drugs, is an antiviral agent targeting and competitively inhibiting viral RNA-dependent RNA polymerase; it is approved in Japan for the treatment of influenza [2]. In some countries, Favipiravir is still in use for the treatment of SARS-CoV-2; however, there is no consensus on its effectiveness in treatment of COVID-19 yet. Therefore, we aim to review the published data regarding the use of Favipiravir in moderate and severe COVID-19 patients. Our live systematic review system will allow the addition of the new findings and provide the results promptly.

Methodology

Search strategy

We systematically reviewed the available literature and presented it using PRISMA (Preferred Reporting Items

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for Systematic Reviews and Meta-Analyses) guidelines [3]. Until June 1, 2021, we searched the following sources using the keywords "Favipiravir" and terms synonymous with COVID-19: PubMed, bioRxiv, medRxiv, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), and Google Scholar.

We included randomized and observational clinical trials that were conducted to investigate the effectiveness of Favipiravir for COVID-19 patients. Studies comparing Favipiravir versus standard of care; different dosages of Favipiravir versus each other; Favipiravir in combination with ineffective agents versus Favipiravir alone were eligible. We avoided gray literature, case series and observational studies without control groups, and randomization. Eventual decision whether or not to include the study in the systematic review was given by two principal investigators in consideration of eligibility criteria. We included the studies with moderate and severe patients, and excluded the ones with critical patients according to the WHO guidelines [4].

Data abstraction and risk of bias assessment

Investigators abstracted data about study design, intervention type, population of control and experimental groups, the stage of the clinical condition, and outcome measures on a Microsoft Excel file. Risk of bias assessment was carried out using Revised Cochrane risk of bias tool for randomized trials (RoB 2) [5] and ROBINS-I assessment tool for non-randomized studies [6]. RoB 2 consists of the following five components: risk of bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. We defined the low risk of bias, if all components of the tool were rated as low. ROBINS-I is composed of seven components: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result. All components must be rated as at low risk of bias for overall study to be at low risk. If there is not any component with serious or critical risk, moderate risk in at least one component is enough to rate the study as at moderate risk of bias.

Data analysis

Primary outcome measures were defined as fatality rates and requirement of ventilation in moderate and severe COVID-19 patients. Heterogeneity assessment was done using the I-squared (I^2) test. For outcome estimation, odds ratio is calculated whenever appropriate with 95% Confidence Interval (CI). Fixed and random effect models were used. Forest plot was used to visualize outcome estimation. As new results come out from the upcoming clinical trials, they will be included in our live meta-analysis.

Results

We identified 2702 studies with our keywords, 2420 studies directly from database search, and 282 studies from other sources such as bioRxiv and medRxiv. After removing 1193 duplicates, we screened titles and abstracts of 1509 studies. Overall, 88 studies were chosen for further analysis, and 1421 studies were excluded due to irrelevant content. We assessed full-text articles of 88 studies for eligibility and included 12 articles in quantitative synthesis (Fig. 1).

Overview of randomized results

Risk of bias assessment of the included studies was reported in Table 1. Among the randomized studies, one study [7] has low risk, six studies [8–14] have moderate risk, and two studies [15, 16] have high risk. Observational studies [14, 17] are identified as moderate risk, and non-randomized study [18] is found to have serious risk.

When studies were investigated from intervention and comparator perspective, two trials compared 1600 mg or 1800 mg of Favipiravir with a patient group treated according to the Russian guidelines [8, 11]. Three trials compared Favipiravir with standard supportive care and one of these administered other antiviral medications outside of Favipiravir [14, 16, 17]. Three trials compared Favipiravir with Hydroxychloroquine [7, 9, 13], one compared with Chloroquine [12], two compared with Lopinavir/Ritonavir [10, 18], and one compared with Umifenovir (Arbidol) [15]. Favipiravir was used in varying doses (Table 2). In all studies, the proportion of male patients was higher. The mean age usually was below the age of 65. According to patients' baseline severity characteristics, four studies [8, 11, 13, 18] included only moderate patients. Three studies [7, 12, 16] included mild-to-moderate patients, and five studies [9, 10, 14, 15, 17] included moderate-to-severe patients.

We performed two meta-analyses for the effectiveness of Favipiravir administration on moderate and severe COVID-19 patients, one on mortality rates by comparing the intervention and comparator groups and one on the requirement of mechanical ventilation by comparing the intervention and comparator groups. In the meta-analysis on fatality rates, only seven studies were suitable for odds ratio calculation (OR 1.11, 95% CI 0.64–1.94). No heterogeneity was detected among these studies ($I^2 = 0\%$, $\tau^2 = 0$; $p = 0.69$) (Fig. 2).

Secondly, we performed a meta-analysis on the requirement of mechanical ventilation, the odds ratio could

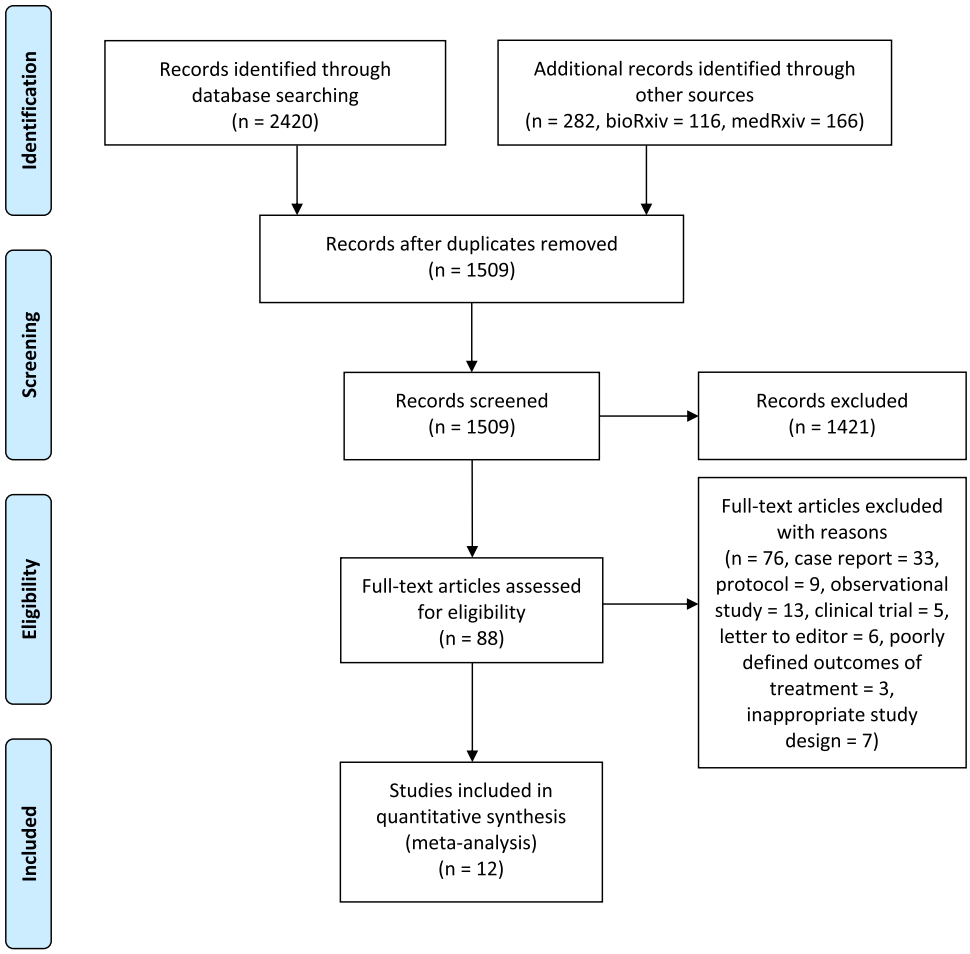

Fig. 1 Search strategy

Table 1 Risk assessment

Study, year (reference)	Study type; risk of bias	Participants, n	Country
Ivashchenko et al., 2020 [8]	Open label; moderate risk of bias	60	Russia
Pushkar et al., 2020 [11]	Open label; moderate risk of bias	200	Russia
Udwadia et al., 2020 [16]	Open label, randomized; high risk of bias	150	India
Khamis et al., 2020 [9]	Open label, randomized; moderate risk of bias	89	Oman
Lou et al., 2020 [10]	Open label; moderate risk of bias	20	China
Chen et al., 2020 [15]	Open label, randomized; high risk of bias	240	China
Szabo et al., 2020 [17]	Observational; moderate risk of bias	150	Hungary
Cai et al., 2020 [18]	Open label, non-randomized; serious risk of bias	80	China
Dabbous et al., 2021a [12]	Open label; moderate risk of bias	92	Egypt
Dabbous et al., 2021b [7]	Open label; low risk of bias	100	Egypt
Balykova et al., 2020 [13]	Open label; moderate risk of bias	39	Russia
Alamer et al., 2021 [14]	Observational; moderate risk of bias	416	Saudi Arabia

be calculated for only five studies (OR 0.50, 95% CI 0.13–1.95). The heterogeneity of these studies was significant ($I^2 = 75\%$, $\tau^2 = 1.5665$; $p < 0.01$) (Fig. 3).

Discussion

Our meta-analysis was focused on two primary outcomes: the effect of Favipiravir on fatality and mechanical

Table 2 Characteristics of the patients

Intervention and comparator	Patients	Baseline characteristics	Baseline severity of patients
Ivashchenko et al., 2020 [8] I-1: (n = 20) Avifavir (1600 mg*2/first day followed by 600 mg*2/day) for 14 days I-2: (n = 20) Avifavir 1800 mg*2/first day followed by 800 mg*2/day) for 14 days C: (n = 20) Standard of care (Drugs recommended in Russian guidelines for the prevention, diagnosis, and treatment of COVID-19.)	The eligible patients included hospitalized men and non-pregnant women of 18 years or older who had moderate PCR-confirmed COVID-19	Not provided	Moderate: 100%
Pushkar et al., 2020 [11] I: (n = 100) Favipiravir (Areplivir) (1600 mg*2/first day followed by 600 mg*2/day) for 14 days C: (n = 100) SOC (Drugs recommended in Russian guidelines for the prevention, diagnosis, and treatment of COVID-19.)	Patients diagnosed as COVID-19 pneumonia; aged between 18 and 80 years; nasopharyngeal swabs samples tested positive for the novel coronavirus RNA	(I) Male: 51%, Mean age: 49.38 (C) Male: 46%, Mean age: 49.98	Moderate: 100%
Udwadia et al., 2020 [16] I: (n = 75) Standard supportive care (antipyretics, cough suppressants, antibiotics, and vitamins) + Favipiravir (1800 mg*1/first day followed by 800 mg*1/day) for 14 days C: (n = 75) standard supportive care	Patients diagnosed as COVID-19 pneumonia; aged between 18 and 75 years; infection with SARS-CoV-2 virus confirmed by RT-PCR within 48 hour prior to randomization	(I) Male: 70.8%, Mean age: 43.6 (C) Male: 76%, Mean age: 43	(I) Mild: 61.1%, Moderate: 38.9% (C) Mild: 60%, Moderate: 40%
Khamis et al., 2020 [9] I: (n = 44) Favipiravir, (1600 mg*1/first day followed by 600 mg*2/day) for maximum 10 days C: (n = 45) Hydroxychloroquine	COVID-19 infected patients age between 18–75 years; confirmed by RT-PCR test on respiratory tract specimens; the interval between symptoms onset and randomization is not > 10 days	(I) Male: 64%, Mean age: 54 (C) Male: 53%, Mean age: 56	Moderate to severe COVID-19 pneumonia
Lou et al., 2020 [10] I: (n = 9) Favipiravir (1600 mg*1/first day followed by 600 mg*3/day) for 14 days + Lopinavir/Ritonavir or Darunavir/Cobicistat and Arbidol C: (n = 10) Lopinavir/Ritonavir or Darunavir/Cobicistat and Arbidol	COVID-19 infected patients confirmed by polymerase chain reaction assay; durations from disease onset to enrolment were 8.5 days (Intervention) and 13.6 days (Comparator)	(I) Mean age: 58.0, Male: 77% (C) Mean age: 46.6, Male: 70%	(I) Moderate: 55%, Severe: 22%, Critical: 22% (C) Moderate: 50%, Severe: 40%, Critical: 10%
Chen et al., 2020 [15] I: (n = 116) Conventional therapy+ Favipiravir (1600 mg*2/first day followed by 600 mg*2/day) for 10 days C: (n = 120) Conventional therapy + Umifenovir (Arbidol)	Patients diagnosed as COVID-19 pneumonia; aged 18 years or older whose initial symptoms were within 12 days	(I) Male: 50.86% <65y: 75% (C) Male: 42.50% <65y: 65.83%	(I) Moderate: 84.48%, Severe: 13.79%, Critical: 1.72% (C) Moderate: 92.50%, Severe: 6.67%, Critical: 0.83%
Szabo et al., 2020 [17] I: Standard of care + Favipiravir (1600 mg*2/first day followed by 600 mg*2/day) for minimum of 10 days C: Standard of care ± other antiviral medications without FVP	COVID-19 infected patients (≥ 18 years of age) confirmed by polymerase chain reaction assay	(I) Male: 49.3%, Mean age: 71.5 (C) Male: 52%, Mean age: 61.0	(I) Moderate: 53.3%, Severe: 46.7% (C)Moderate: 45.3%, Severe: 54.7%

Table 2 (continued)

Intervention and comparator	Patients	Baseline characteristics	Baseline severity of patients
Cai et al., 2020 [18] I: (n = 35) Favipiravir (1600 mg*2/first day followed by 600 mg*2/day) for 14 days or until viral clearance C: (n = 45) Lopinavir/Ritonavir	COVID-19 infected patients aged 16–75 years old; nasopharyngeal swabs samples tested positive for the novel coronavirus RNA; duration from disease onset to enrolment was less than seven days	(I) Mean age: 43, Male: 40% (C) Mean age: 49, Male: 46.7%	Moderate: 100%
Dabbous et al., 2021a [12] I: (n = 44) Standard of care therapy + Favipiravir (1600 mg*2/first day followed by 600 mg*2/day) for 10 days C: (n = 48) Standard of care therapy + Chloroquine	COVID-19 infected patients aged between 18 and 80 years; duration from disease onset to enrolment was three days	(I) Mean age: 29, Male: 45.5% (C) Mean age: 34, Male: 52.1%	(I): Mild and moderate, Comorbidities: 25% (C): Mild and moderate, Comorbidities: 12.5%
Dabbous et al., 2021b [7] I: (n = 50) Favipiravir (3200 mg*1/first day followed by 600 mg*2/day) for 10 days C: (n = 50) Hydroxychloroquine (800 mg*1/first day followed by 200*2/day) and oral oseltamivir (75 mg*2/day) for 10 days	COVID-19 patients aged between 18 and 80 years; confirmed by diagnostic laboratory tests (e.g. nasopharyngeal swab)	(I) Mean age: 36.3, Male: 50% (C) Mean age: 36.4, Male: 50%	mild to moderate
Balykova et al., 2020 [13] I: (n = 17) Favipiravir (1600 mg*2/first day followed by 600 mg*2/day) for 13 days C: (n = 22) Hydroxychloroquine(400 mg*2/first day followed by 200*2 for 6 days) or Lopinavir/Ritonavir(400 mg + 100 mg orally every 12 h for 14 days)	Patients diagnosed as COVID-19 pneumonia; aged between 18 and 80 years; nasopharyngeal swabs samples tested positive for the novel coronavirus RNA	(I) Mean age: 47.12 ± 2.26 years (C) Mean age: 47.5 ± 1.99 years	Moderate: 100%
Alamer et al., 2021 [14] I: (n = 220) two doses of FPV (1800 mg*2 or 1600 mg*2/first day followed by 800 mg or 600 mg/day BID C: (n = 196) Standard of care	Patients diagnosed as infected with SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab	(I) Mean age: 50.3, Male: 60% (C) Mean age: 52.5, Male: 60%	Moderate: 30.9%, Severe: 60.4%

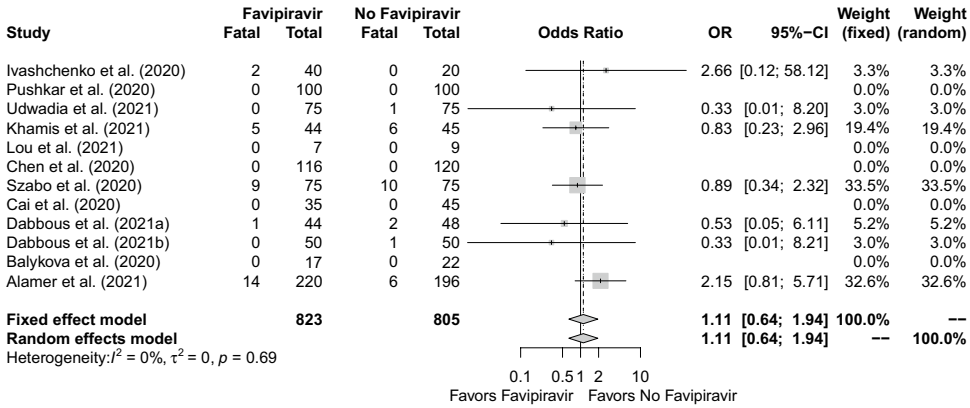

Fig. 2 Forest plot for the effectiveness of Favipiravir on fatality compared to standard of care

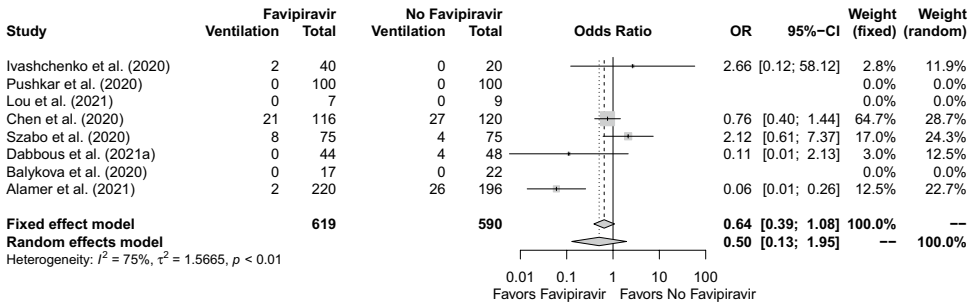

Fig. 3 Forest plot for the effectiveness of Favipiravir on the need for mechanic ventilation compared to standard of care

ventilation. Our findings revealed that Favipiravir, for up to 14 days, has no superiority over standard of care or other antivirals that are previously shown to be ineffective for COVID-19 such as hydroxychloroquine [19, 20], chloroquine [21], Lopinavir/Ritonavir [22], and Arbidol [23] (Figs. 2 and 3). Notably, in the meta-analysis for mechanical ventilation, we detected significant heterogeneity, which indicates the diversity of clinical studies included. This finding is in favor of our report of moderate to high risk of bias in these studies.

All of our selected studies except Dabbous et al. [7] were identified as either moderate or high risk of bias. Having moderate or high risk of bias was the major limitation for the studies included, however we included all the available reports.

In vitro effectiveness of Favipiravir against SARS-CoV-2 is controversial. Wang et al. [24] reported an EC50 value of 61.88 µM for the antiviral activity of Favipiravir, while results from Pizzorno et al. [25] and Choy et al. [26] showed no inhibition at 100 µM, which was the highest concentration tested in an antiviral assay. Results from Lou et al. [10] showed that less than 50% of SARS-CoV-2 had been affected in vitro at Favipiravir concentrations up to 100 µM. Moreover, the intracellular concentration of the active metabolite determines the efficacy of Favipiravir in patients [27]. In vivo intracellular simulations conducted by Pertinez et al. [28] indicated that a loading dose of 1600 mg twice daily on day 1 followed by a maintenance dose of 1200 mg twice daily for nine days could reach the therapeutic concentrations of the intracellular active metabolite of Favipiravir. However, further studies are needed for pharmacokinetics of Favipiravir.

Although, at the beginning of the pandemic, it was believed that viral load measurements and viral clearance were appropriate to follow disease progress in COVID-19 patients [23], learning more about SARS-CoV-2 has shown that viral load as an outcome is not a good choice to measure the treatment efficacy. Many patients continued to have positive RNA tests, even after they have unequivocally recovered [29]. As a result, CDC has updated the definition of recovery as being symptom-free for over 24 h after symptom onset [30]. Therefore, we think that viral load measurements would not be a proper indicator of the effectiveness of Favipiravir, and we did not include it in our meta-analysis. Subsequently, we did not include the clinical improvement data in our meta-analysis, because the definition of this concept differs among studies and leaves the clinical improvement being a subjective concept. However, incorporating a brief overview of findings regarding the viral clearance and the clinical improvement into the discussion part could be beneficial. Seven studies have reported viral clearance as an outcome, but there are some methodological differences between them in the assessment of viral clearance. Ivashchenko et al. [8] and Pushkar et al. [11] found that viral clearance is higher in the Favipiravir group at day 10. Lou et al. [10] found that viral clearance was higher

in the Favipiravir group on day 14. Additionally, Udwadia et al. [16] and Cai et al. [18] found that median days for viral clearance was lower in Favipiravir group than control, showing that the viral clearance was better with Favipiravir treatment. Balykova et al. [13] found no significant difference between control and Favipiravir group in viral clearance since all patients were negative at day 10. On the other hand, Szabo et al. [17] found that median days for viral clearance was higher in the Favipiravir group indicating that Favipiravir does not have any significant effect on viral clearance. According to the study of Zhao et al. [31] conducted on patients with SARS-CoV-2 re-positive after discharge, the Favipiravir group experienced faster viral clearance than the control group. Four studies [8, 11, 13, 18] have investigated the improvement rates of chest CT scans. Ivashchenko et al. [8] and Pushkar et al. [11] reported that there was no significant difference between Favipiravir and control arm in terms of chest CT improvement on day 15. Balykova et al. [13] and Cai et al. [18] reported that the improvement rates of the chest CT changes were higher in the Favipiravir arm on day 15. Four studies [8, 11, 13, 15] investigated body temperature normalization. Chen et al. [15], Blaykova et al. [13], and Ivashchenko et al. [8] found that the time to pyrexia relief was shorter in the Favipiravir arm. However, Pushkar et al. [11] found that there is not a significant difference between Favipiravir and control arm in terms of body temperature recovery time. Four studies [10, 11, 15, 16] investigated clinical improvement. On day 14, clinical improvement was not significantly different between Favipiravir and the control arm according to Udwadia et al. [16] and Lou et al. [10]. Pushkar et al. [11] and Chen et al. [15] found that clinical status improvement rate was significantly higher in the Favipiravir group on day 14 and day 7, respectively.

We excluded the studies that compared the critical patients who stayed in ICU, because the effect of antivirals can be seen at the first week of the disease. Relatedly, we did not include the duration of stay in the intensive care unit (ICU) in the analysis. Nevertheless, summarizing the findings related to critical patients could give an insight into the effectiveness of Favipiravir in those patients. In the study of Lou et al. [10], there were two critical patients in the Favipiravir group and one critical patient in the control group. Although the patient in the control group and one of the patients in the Favipiravir group had viral clearance in 14 days, the other patient in the Favipiravir group could not turn viral negative in 14 days. Alamer et al. [14] compared the mortality and median time to discharge among critical patients in Favipiravir and control groups. The median time to discharge is 21 and 32 in Favipiravir and control groups, respectively. Whereas the fatality rates are given as 46.2% in the Favipiravir group and 25.9% in the control group. Takahashi et al. [32] reported two critical patients, who started Favipiravir on day 11 after symptom onset. Patients turned viral negative in 18 and 13 days, respectively, and experienced chest imaging improvement.

There are several limitations of our analysis. The scarcity of the randomized clinical trials narrows the sample size of our analysis. Moreover, it is hard to conduct a large-scale clinical trial in this pandemic due to the lack of patients without any previous treatment. Some observational studies are not prospective while some clinical trials are not controlled. In our analysis, all clinical trials are open label and one of them is not a randomized study. Another limitation was the variation in the definitions of patient severity. In two studies, few critical patients were included. In Lou et al. [10], results of critical patients were removed but it was not feasible to separate the data of critical patients in Chen et al. [15]. We did not exclude it since the percentage of critical patients was very limited (Table 2). There is heterogeneity in the control groups and there is no study done against placebo. Nevertheless, drugs used in control groups are proven not to be effective against COVID-19. Risk factors that can increase mortality rate are not specified in some studies. Results of this meta-analysis cannot be applied to patients with severe renal or hepatic dysfunction and pregnant women because they were not included in clinical trials and the observational study.

In some countries, COVID-19 treatment guidelines suggested Favipiravir as an antiviral drug proven to be safe and effective in vitro. Based on published data and literature, the countries that use Favipiravir are China, Hungary, India, Korea, Poland, Portugal, Russia, Serbia, Thailand, and Turkey. By June 1, 2021, 52 active trials in countries including Italy, Saudi Arabia, Indonesia, Kuwait, USA, Iran, Nepal, Canada, Bahrain, Egypt, UK, Thailand, Australia, South Africa, and Germany were registered in clinicaltrial.gov [33]. Among these studies, 13 of them had a completed status, and one completed study with published results has been included in this meta-analysis. In a recent meta-analysis performed for the effectiveness of Favipiravir, the authors [34] reported that Favipiravir had no significant beneficial effect on the mortality among mild to moderate COVID-19 patients. The authors stated that the late administration of antivirals could explain their low effectiveness. However, in some countries e.g. Turkey, Favipiravir is provided by the Ministry of Health and administered early in the disease course and no significant benefit has been reported yet.

Conclusion

There is no evidence that Favipiravir decreases the fatality rate or the use of mechanical ventilation among moderate and severe patients with COVID-19. Randomized clinical trials or quality observational studies including moderate

and severe patients with appropriate sample sizes are needed for describing the effectiveness of Favipiravir in COVID-19.

Acknowledgements We are thankful to Ertaç Nebioğlu from Koç University Health Sciences Library for his effort on systematic literature search.

Author contribution Literature search: BÖ, ŞKo, REA, MK, DY, İBP, ŞKe, ÖE.
Data analysis: BÖ, ŞKo, REA, MK, DY, İBP, ŞKe, MG, ÖE
Manuscript writing: BÖ, ŞKo, REA, MK, DY, İBP, ŞKe, MG, ÖE

Data availability All the data for analysis is available.

Code availability The codes of the software application (R) are available.

Declarations

Ethics approval and consent to participate The analysis of systematic review is exempt from IRB review.

Conflict of interest The authors declare no competing interests.

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