Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Future of antivirals in COVID-19: The case of favipiravir

We appreciate the publication of the randomized controlled trial by Solaymani-Dodaran et al. [1], which aimed to determine the effect of favipiravir on the clinical outcomes among patients with moderate-to-severe course of COVID-19. It was reported from the randomized trial that patients with COVID-19 who were randomized to favipiravir, which is an antiviral agent that selectively and potently inhibits the RNA-

Table 1
Characteristic of included studies.

Study (year)	Study design	Country	Age (median/mean)	Number of days since symptom onset	Regimen of favipiravir in the intervention group	Regimen of comparative intervention in the control group	Mortality		Risk of bias[1]
							Favipiravir users (n/N; %)	Non-favipiravir users (n/N; %)	
Bosaeed et al. [2] (2021)	Open label, randomized controlled trial	Saudi Arabia	Favipiravir users = 53.0 Non-favipiravir users = 52.3	Favipiravir users = 6.0 Non-favipiravir users = 5.8	Favipiravir 1800 mg twice on day 1 followed by 800 mg twice daily for 10 days + hydroxychloroquine + standard care	Standard care (glucocorticoids, other immunomodulators, and antibiotic agents)	14/125; 11.2	15/129; 11.6	Some concerns
Solaymani-Dodaran et al [1] (2021)	Open label, randomized controlled trial	Iran	Favipiravir users = 58.6 Non-favipiravir users = 56.6	N/A	Favipiravir 1600 mg once followed by 600 mg every 8 h for 7 days + hydroxychloroquine	Hydroxychloroquine + lopinavir/ritonavir	26/190; 13.7	21/183; 11.5	Some concerns
Khamis et al [4] (2021)	Open label, randomized controlled trial	Oman	Favipiravir users = 54.0 Non-favipiravir users = 56.0	N/A	Favipiravir 1600 mg once on day 1 followed by 600 mg twice daily for a maximum of 10 days + interferon beta-1b	Hydroxychloroquine	5/44; 11.4	6/45; 13.3	Some concerns
Atipornwanich et al [5] (2021)	Open label, randomized controlled trial	Thailand	Favipiravir users = 47.3 Non-favipiravir users = 44.8	Favipiravir users = 6.7 Non-favipiravir users = 6.0	Favipiravir 6000 mg on day 1 followed by 2400 mg daily for 7–14 days + lopinavir/ritonavir or darunavir/ritonavir ± hydroxychloroquine	Oseltamivir + lopinavir/ritonavir or darunavir/ritonavir ± hydroxychloroquine	10/50; 20.0	13/50; 26.0	Some concerns
Shenoy et al [6] (2021)	Randomized, double-blind, controlled trial	Kuwait	N/A	Favipiravir users = 6.3 Non-favipiravir users = 6.2	Favipiravir 1800 mg twice on day 1 followed by 800 mg twice daily for 10 days	Placebo	14/175; 8.0	3/24; 6.2	
Chuah et al [3] (2021)	Open label, randomized controlled trial	Malaysia	Favipiravir users = 62.6 Non-favipiravir users = 62.4	Favipiravir users = 5.0 Non-favipiravir users = 5.2	Favipiravir 1800 mg twice on day 1 followed by 800 mg twice daily for 5 days + standard care	Standard care	5/250; 2.0	0/250; 0	Some concerns

[1] Risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials.

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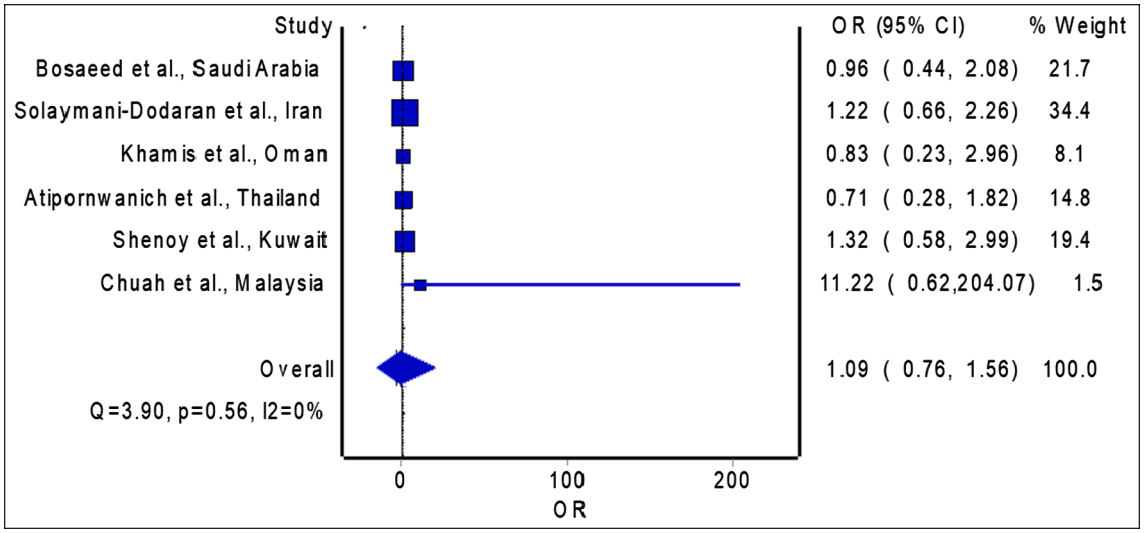

Fig. 1. Pooled odds of mortality with the use of favipiravir among patients with COVID-19 relative to non-use of favipiravir.

dependent RNA polymerase of RNA viruses, had no significant difference in terms of mortality rate, compared to their counterparts who were randomized to lopinavir/ritonavir (favipiravir group: 13.7% versus lopinavir/ritonavir group: 11.5%; P = 0.52). The trial [1] might be underpowered to detect mortality differences; since there have been few trials that reported the association between the use of favipiravir and the risk of mortality in patients with COVID-19, we summarized the overall evidence in the form of meta-analysis from all the randomized trials which reported mortality outcomes with the use of favipiravir in patients with COVID-19.

We performed systematic literature search in electronic databases, including PubMed, Google Scholar, Cochrane Central Register of Controlled Trials, and preprint servers to identify eligible studies published up to November 25, 2021. Studies eligible for inclusion were randomized controlled trials that reported the risk of mortality with the use of favipiravir in patients with COVID-19 relative to non-use of favipiravir. Meta-analysis with the random-effects model was used to estimate the pooled odds ratio of mortality with the use of favipiravir relative to non-use of favipiravir, at 95% confidence intervals (CIs). In addition, we examined the heterogeneity between studies using the I^2 statistics and the χ^2 test, with significant heterogeneity being considered at 50% and $P < 0.10$, respectively. All analyses were performed using Meta XL, version 5.3 (EpiGear International, Queensland, Australia).

Our systematic literature search retrieved 1493 hits, of which 613 were unique. After screening, we included six randomized controlled trials (Table 1) [1–6], with a total of 1669 patients with COVID-19. The meta-analysis of the included trials [1–6] revealed no significant difference in the odds of mortality with the use of favipiravir among patients with COVID-19, relative to non-use of favipiravir; the estimated effect though indicated increased mortality (Fig. 1; pooled odds ratio = 1.09; 95% confidence interval 0.76 to 1.56) but is without adequate evidence against the null hypothesis of 'no significant difference,' at the current sample size.

The absence of mortality benefits with the use of favipiravir in patients with COVID-19 might be attributed to the low plasma concentrations achieved since favipiravir has a complex pharmacokinetic profile. Recently, it has been reported that combined treatment of favipiravir and molnupiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model [7]. Therefore, we believe that future trials should aim to determine the clinical efficacy of such combination instead of favipiravir alone; apart from potentially increased efficacy, such combination could also result in lower doses of both agents to be administered, which can be cost-saving since molnupiravir is relatively expensive. Besides, with lower doses of molnupiravir being administered, the safety profile may be more favorable, especially when there have been some safety concerns with the use of molnupiravir.

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