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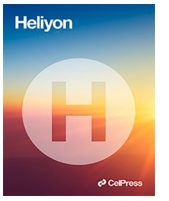

Research article

Favipiravir does not improve viral clearance in mild to moderate COVID-19 – A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Purpose: Favipiravir has been used in the therapy of COVID-19, including patients with mild to moderate symptoms in certain countries. The aim of our systematic review and meta-analysis was to investigate its efficacy and safety in mild-to-moderate COVID-19 infections.
Methods: The PubMed, Embase, Web of Science, and Cochrane databases were systematically reviewed for articles reporting the results of randomized controlled trials published until January 6, 2023, resulting in the identification of 20 eligible studies.
Results: There were no significant differences in viral clearance time (HR = 1.20, p = 0.09) compared to those without favipiravir therapy. However, in the subgroup analyses, favipiravir treatment significantly increased viral clearance by 59 % (HR = 1.59, $p < 0.01$) and 42 % (HR = 1.42, $p < 0.01$], $I^2 = 20$ %) compared to the comparator group in patients with moderate severity of COVID-19 and in the inpatient care setting, respectively. Favipiravir had no beneficial effects in the case of patients with mild symptoms and treated in ambulatory care.
Conclusions: The use of favipiravir is questionable in the treatment of outpatients with COVID-19 with mild symptoms. Moderate beneficial effects in the case of patients with moderate symptoms and inpatients should be treated with care due to the limitations of the analysed trials.

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1. Introduction

Favipiravir, a broad-spectrum antiviral drug, was initially developed for treating influenza. It is phosphoribosylated to its active form, favipiravir-ribofuranosyl-5′-triphosphate, by cellular enzymes, and it inhibits the RNA-dependent RNA polymerase of the influenza virus, thereby it is used to decrease viral load. Favipiravir was approved as a treatment for novel or re-emerging influenza viruses in Japan in 2014. Based on its mechanism of action, it might be effective against other RNA viruses, e.g., Ebola virus, Lassa virus, and rabies [1]. After the outbreak of the COVID-19 pandemic, favipiravir was one of the candidates for antiviral therapy for this disease. However, favipiravir was not approved in countries other than Japan until March 2020, when it was officially recommended in China to treat COVID-19 infection. In June 2020, India also approved favipiravir with the same indication [2].

The clinical efficacy of favipiravir in COVID-19 infection was first studied in China however, these (and other early) studies had several weaknesses (e.g. lack of randomization and blinding, heterogenous study population) [3,4]. Later, the number of registered or published clinical trials increased rapidly, and favipiravir was authorized for emergency or compassionate use in several countries, including Bangladesh, Egypt, Hungary, Japan, Kazakhstan, Moldova, Russia, Saudi Arabia, Thailand, Turkey, Ukraine, United Arab Emirates, and Uzbekistan [5,6].

As other potentially effective antiviral agents appeared on the market or were subjected to clinical trials (e.g., remdesivir, molnupiravir, paxlovid) and the studies with favipiravir did not unequivocally support the efficacy of this pharmacon, the position of favipiravir changed in the majority of the therapeutic guidelines. Furthermore, favipiravir has remained unapproved by the Food and Drug Administration of the United States of America and the European Medicines Agency to treat COVID-19. Since the outbreak of the COVID-19 pandemic, several clinical trials have been conducted, and the efficacy of favipiravir has also been assessed in meta-analyses. However, previous meta-analyses did not assess the efficacy of favipiravir on viral clearance time as the primary outcome measure. Our aim was to systematically review the literature and analyse the clinical efficacy and safety of favipiravir in mild to moderate COVID-19.

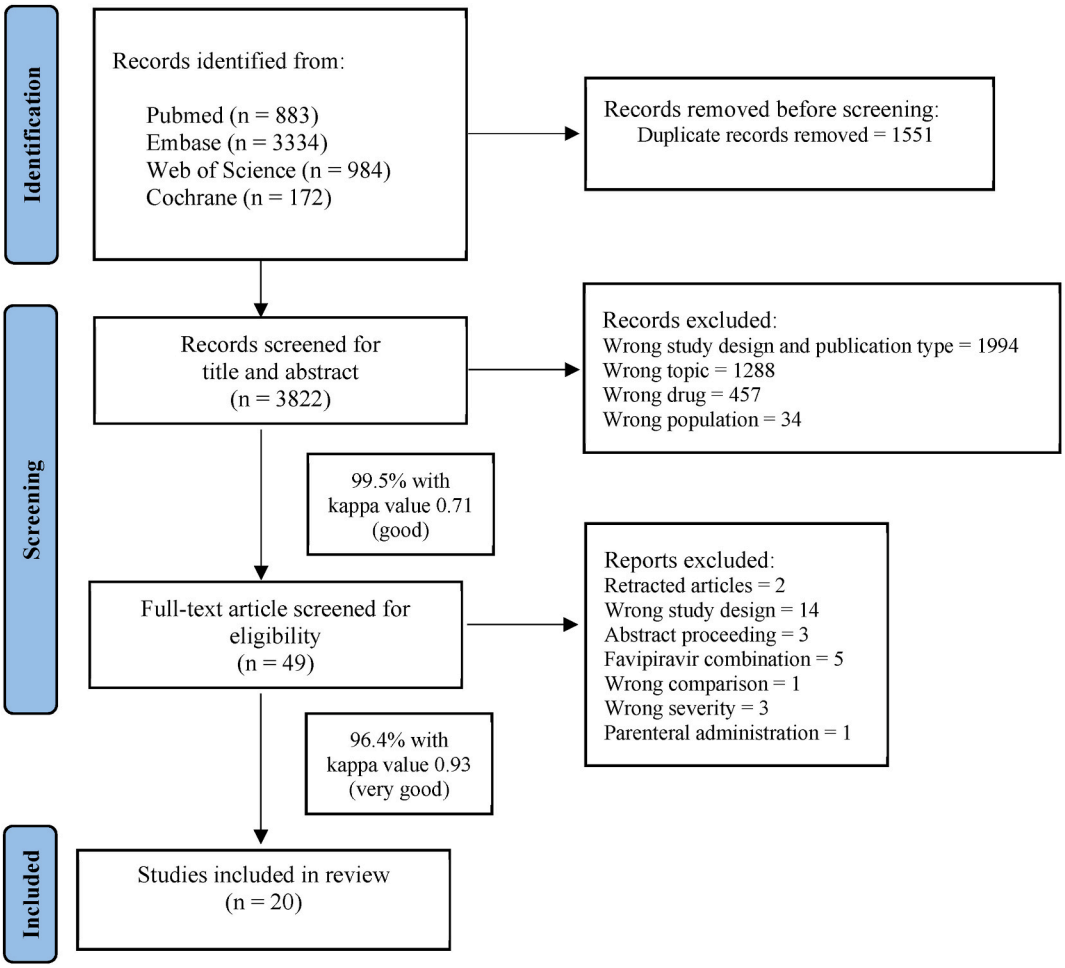

Fig. 1. Flow chart of study selection.

Table 1
Characteristics of eligible studies.

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir	Comparator	Onset to randomization
			Favipiravir (F)	Comparator (C)	Mean in years (SD)	Median in years (IQR)	Quantity (<65 years, %)						
Abdur Rahman, 2022[42]	Bangladesh	Double-blinded randomized controlled trial	25	25	F: 37.96 (11.45) C: 37.54 (10.18)			F: 64 C: 68	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	Placebo	Within 7 days
AlQahtani, 2022[37]	Bahrain	Randomized, controlled, open-labeled study	54	51		F: 44.5 (33.0, 50.0) C: 48.5 (35.5, 57.0)		F: 43 C: 52	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 10th day: 600 mg (bid)	SoC	Within 10 days
Balykova,2020a[38]	Russia	Randomized, open-label, multicenter comparative study	17	22	F: 47.1 (2.3) C: 47.5 (1.9)			No Information	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th days: 600 mg (bid)	SoC treatment of COVID-19 in Russian guideline	Hospitalization not exceeding 48 h before administration of favipiravir
Balykova, 2020b[39]	Russia	Open randomized multicentre comparative study	100	100	Mean age of population: 49.7 (13.1) Range of age: 20 to 80			F: 50.9 C: 49.0	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th day: 600 mg (bid)	SoC treatment of COVID-19 in Russian guideline	Hospitalized not more than 48 h before the start of the study
Bossaed, 2021[30]	Saudi Arabia	Randomized double-blinded, multicentre placebo-controlled trial	112	119		F: 37 (31.5, 45.0) C: 37 (32, 44)		F: 64.2 C: 69.7	Mild	Outpatient	1st day: 1800 mg (9 tab) (bid) 2nd – 5th or 7th days: 800 mg (bid)	SoC + Placebo	Within 5 days of disease onset
Chen, 2021[4]	China	Randomized controlled, open-label multicenter trial	116	120			F: 75 C: 65.8	F: 50.9 C: 42.5	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 7th days: 600 mg (bid)	SoC + Umifenovir: 200 mg (tid)	Within 12 days of initial symptoms
Chuah, 2022[45]	Malaysia	Randomized, open-label, parallel, multicenter, phase 3 clinical trial	250	250	F: 62.6 (7.51) C: 62.4 (8.41)			F: 52.4 C: 44.4	Mild to moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 5th days: 800 mg (bid)	SoC	Within 7 days
Golan, 2022[43]	USA, Brazil, Mexico	Randomized, multicenter, double-blinded, placebo-controlled trial	599	588			F (<60, %): 84.5 C (<60, %): 86.1	F: 47.1 C: 44.4	Mild to moderate	Outpatient	1st day: 1800 mg (bid) 2nd – 10th days: 800 mg (bid)	Placebo + SoC	Within 5 days
Holubar, 2021[31]	USA	Randomized, double-blind, placebo-	59	57	F: 42.9 (12.3) C: 43.4 (12.8)			F: 52.5 C: 49.1	Mild	Outpatient	1st day: 1800 mg (bid) 2nd – 10th	Placebo + SoC	Positive SARS-CoV2 RT-PCR

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Table 1 (*continued*)

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir	Comparator	Onset to randomization
			Favipiravir (F)	Comparator (C)	Mean in years (SD)	Median in years (IQR)	Quantity (<65 years, %)						
		controlled phase 2 trial									day: 800 mg (bid)		within 72 h of enrollment
Ivashchenko, 2020[40]	Russia	Randomized, adaptive, multicenter, open-label, Phase II/III clinical trial	40	20		No information		No information	Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 14th days: 600 mg (bid) or 1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	SoC	No information
Lou, 2021[41]	China	Randomized, exploratory single-center, open-label, controlled trial	9	10	F: 58.0 (8.1) C: 46.6 (14.1)			F: 77 C: 70	Mild to Moderate	Inpatient	1st day: 1600 mg or 2200 mg (tid) 2nd – 14th days: 600 mg (tid)	SoC	No information
Lowe, 2022[28]	UK	Randomized, Double-blind, 2x2 factorial placebo-controlled trial	59	60	F: 40.3 (12.1) C: 40.6 (12.2)			F: 54.2 C: 51.7	Mild	Outpatient	1st day: 1800 mg (bid) 2nd – 7th day: 400 mg (qid)	Placebo + SoC	Within 7 days of symptom onset
McMahon, 2022[47]	Australia	Randomized placebo-controlled phase 2 trial	66	67		F: 36 (28–49) C: 35 (27.5, 52.5)		F: 55.6 C: 54	Mild and Moderate	Inpatient and Outpatient	1st day: 1800 mg (bid) 2nd – 14th day: 800 mg (bid)	Placebo + SoC	Within 5 days
Ruzhentsova, 2021[32]	Russia	Randomized, open-label, active-controlled trial	112	56	F: 41.7 (10.6) C: 42.0 (10.4)			F: 43.8 C: 53.6	Mild and Moderate	Inpatient and Outpatient	1st day: 1800 mg (bid), 2nd – 9th day: 800 mg (bid)	SoC	No more than 6 days
Shenoy, 2021[46]	Kuwait	Randomized, multicentre, double-blind, placebo-controlled, parallel design	175	178			F (<50, %): 40 C (<50, %): 41.6	F: 67.4 C: 67.4	Moderate	Inpatient	1st day: 1800 mg (bid), 2nd – 10th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Shinkai, 2021[33]	Japan	Randomized, single-blind, placebo-controlled, parallel-group design	107	49	F: 43.8 (12.5) C: 48.7 (14.1)		F: 94.4 C: 85.7	F: 71.0 C: 57.1	Moderate	Inpatient	1st day: 1800 mg (bid) 2nd – 13th day: 800 mg (bid)	Placebo + SoC	Within 10 days
Sirijatuphat, 2022[36]	Thailand	Multicentre, open-labeled,	62	31		F: 32 (27–39)		F: 33.9 C: 38.7	Mild	Inpatient	1st day: 1800 mg (bid) 2nd – 14th	SoC	Within 10 days

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Table 1 (*continued*)

Ref.	Country	Study Design	Number of patients		Age			Sex (Male in %)	Severity	Setting of care	Favipiravir	Comparator	Onset to randomization
			Favipiravir (F)	Comparator (C)	Mean in years (SD)	Median in years (IQR)	Quantity (<65 years, %)						
		randomized control study				C: 28 (25, 35)					day: 800 mg (bid)		
Tehrani, 2022[44]	Iran	Randomized, open-label, controlled clinical trial,	38	40	F: 53.08 (11.80) C: 51.95 (13.34)			F: 52.6 C: 57.5	Moderate	Outpatient	1st day: 1600 mg (bid) 2nd – 4th day: 600 mg (bid)	SoC	Within 3–9 days
Udwadia, 2021[34]	India	Randomized, open-label, parallel-arm, multicenter trial	72	75	F: 43.6 (12.2) C: 43.0 (11.2)			F: 70.8 C: 76.0	Mild and Moderate	Inpatient	1st day: 1800 mg (bid), 2nd – 14th day: 800 mg (bid)	SoC	No more than 7 days
Zhao, 2021[35]	China	Multicenter open-label, randomized controlled trial	36	19	F: 55.8 (13.6) C: 55.5 (12.6)			F: 44.4 C: 47.4	Mild and Moderate	Inpatient	1st day: 1600 mg (bid) 2nd – 7th days: 600 mg (bid)	SoC	No information

SoC: standard of care; bid: two times per day; tid: three times a day; qid: four times per day.

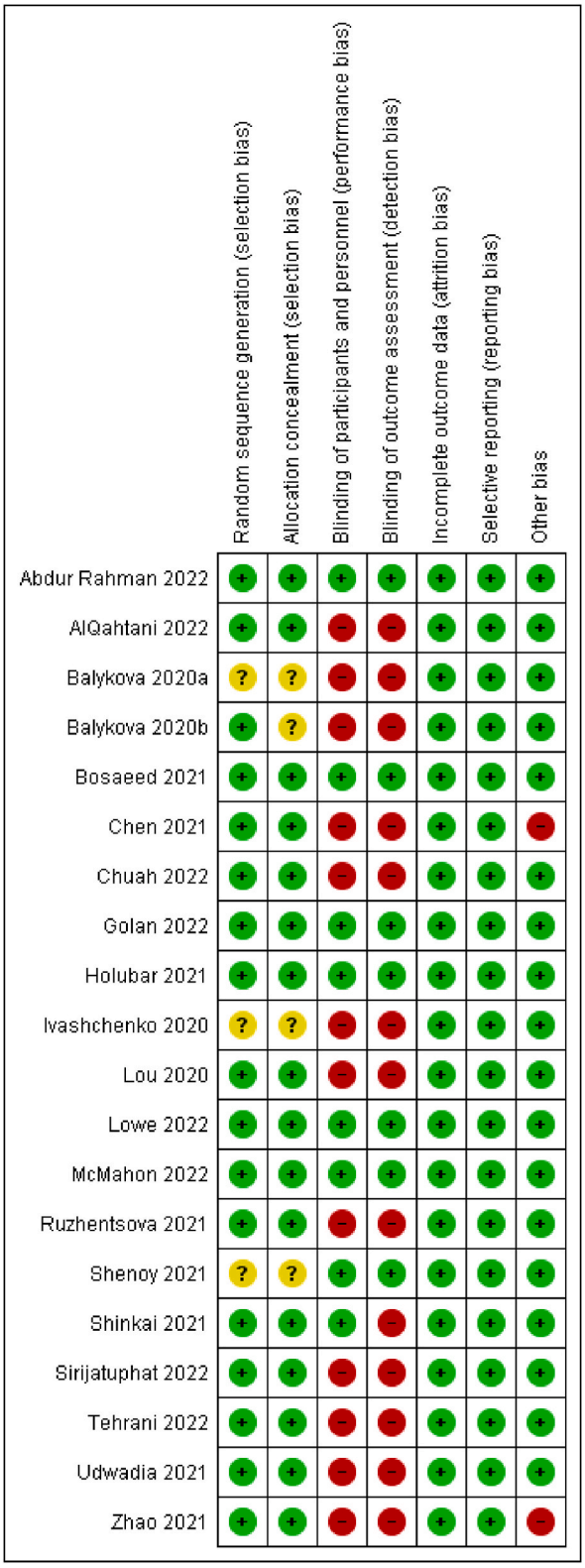

Fig. 2. Risk of bias summary of included studies.

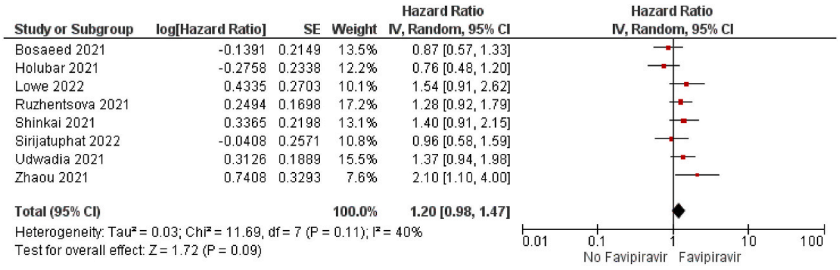

Fig. 3. Favipiravir has no significant effect on viral clearance compared to comparator.

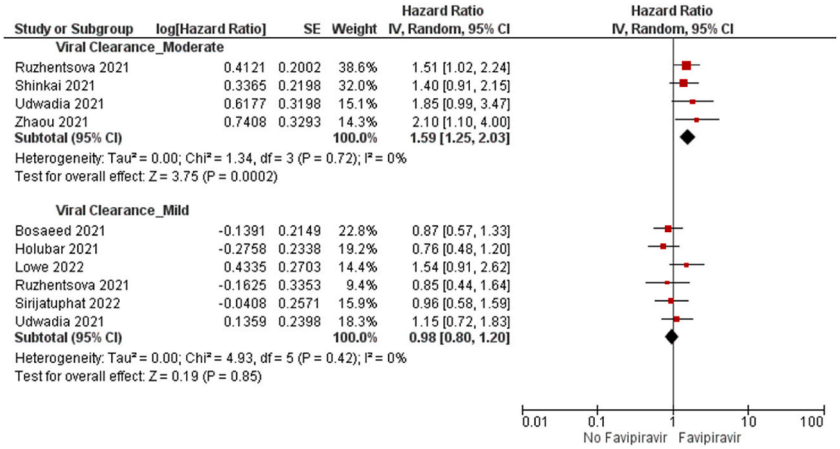

Fig. 4. Favipiravir is more effective in terms of viral clearance in moderate, but not in mild severity.

2. Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement was used to guide the report of this meta-analysis [7]. The study protocol was prospectively registered in PROSPERO under the reference number CRD4202232443 (www.crd.york.ac.uk).

2.1. Inclusion criteria

The patient, intervention, comparison, outcomes, and study design (PICOS) approach was used to answer our clinical questions and applied as follows: P: COVID-19 patients with mild-to-moderate conditions (categorized by the authors of the trials), I: favipiravir, C: placebo/standard of care/another antiviral drug, O: time to viral clearance, S: randomized, controlled trials. The definition of mild and moderate illness in the papers is usually based on the descriptions provided by the World Health Organization (WHO) [8]. Mild patients were 'symptomatic patients (fever, cough, fatigue, shortness of breath, anorexia, etc) without viral pneumonia or hypoxia' and had no imaging findings of pneumonia. Meanwhile, moderate patients were 'patients with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) with no signs of severe pneumonia, including SpO2 $\geq$ 90 % on room air but had imaging findings on pneumonia. Viral clearance was defined as the change in the RT-PCR result from positive to negative in two consecutive tests separated by at least 24 h. Secondary outcomes were clinical recovery rates, the proportion of patients with improvement in chest imaging compared to baseline, death, emergency department visit, hospitalization, admission to the ICU and hospital discharge. Clinical recovery was defined as the improvement in the patient's clinical condition indicated by improvements in respiratory signs and symptoms (such as oxygen saturation, respiratory rate, chest imaging), normalization of body temperature, or improvement in other relevant clinical indicators (for example, WHO category of clinical status) sustained for at least 72 h. Indicators of safety included in this study were the proportion of patients who developed hyperuricemia, low hemoglobin, hyperglycemia, elevated levels of alanine transaminase (ALT) and aspartate aminotransferase (AST), high bilirubin, elevated creatine phosphokinase, high triglycerides, and leukopenia, as well as experiencing symptoms such as abdominal pain, anorexia, constipation, diarrhea, dizziness, dyspnoea, dyspepsia, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash, and vomiting.

Table 2
Effects of favipiravir on clinical improvement.

Reference	Parameters	Results		
		Overall	Mild	Moderate
Favorable for favipiravir (FPV)				
Balykova, 2020b[39]	The proportion of patients who achieved clinical scale ≤2 in the WHO 8-Category Ordinal Scale (transfer to outpatient or complete recovery)			RR: 1.34, 95 % CI: 1.15–1.56 FPV: 90 % SoC: 67 %
Chen, 2021[4]	Clinical recovery rate: based on the recovery of temperature, respiratory rate, oxygen saturation, and cough relief.			RR: 1.28, 95 % CI: 1.04–1.57 FPV: 71.43 % SoC + Umifenovir: 55.86 % Rate ratio: 0.1557 (95 % CI: 0.03–0.28, p value = 0.02)
Ruzhentsova, 2021[32]	Time to a reduction of patient clinical status on at least 1 score according to the WHO 8-Category Ordinal Scale compared to baseline.	HR: 1.63, 95 % CI: 1.14–2.34 Median time FPV: 6 days (IQR: 4–9.25 days) SoC: 10 days (IQR: 5–21 days) RR: 1.26, 95 % CI: 1.02–1.54 FPV: 83.03 % SoC: 66.10 %		HR: 1.66, 95 % CI: 1.09–2.52
Shinkai, 2021[33]	Time to improvement in four clinical parameters: temperature, SpO_2, chest imaging, and viral clearance (two consecutive negative results separated by at least 24 h).			HR: 1.59, 95 % CI: 1.02–2.48 Median time FPV: 11.9 days (95 % CI: 10.0–13.1) Placebo: 14.7 days (95 % CI: 10.5–17.9) RR: 1.32, 95 % CI: 1.02–1.73 FPV: 75.70 % SoC: 57 %
Sirijatuphat, 2022[36]	Time to sustained clinical improvement by a National Early Warning Score (NEWS) of ≤1 for at least 7 days		HR: 2.77, 95 % CI: 1.57–4.88 Median time FPV: 2 days Control: 14 days Range of 1–28 days for both groups RR: 2.45, 95 % CI: 1.45–4.15 FPV: 79 % SoC: 32.3 %	
Tehrani, 2022[44]	Respiratory rate at the end of study (day 7 after treatment)	F: 21.08 ± 2.92 SoC: 19.3 ± 1.60 P < 0.01		
Udwadia, 2021[34]	Time to clinical cure: according to clinician assessment and clinical parameters such as normalization of fever, respiratory rate, oxygen saturation as well as cough relief persisted for ≥72 h.	HR: 1.75, 95 % CI: 1.10–2.79 Median time FPV: 3 days (95 % CI: 3–4 days) Control: 5 days (95 % CI: 4–6 days) RR: 1.02, 95 % CI: 0.94–1.12 FPV: 96.22 % SoC: 93.90 %		HR: 2.09, 95 % CI: 1.06–4.15 Median time FPV: 3.5 days (95 % CI: 3–4 days) Control: 6 days (95 % CI: 4–12 days) RR: 1.09, 95 % CI: 0.92–1.30 FPV: 95.83 % SoC: 87.50 %
Unfavorable for favipiravir (FPV)				
AlQahtani, 2022[37]	The proportion of patients who recovered based on a clinical scale <2 at the end of the study (hospital discharge)	RR: 1.03, 95 % CI: 0.86–1.23 FPV: 83.33 % SoC: 80.77 %		

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Table 2 (*continued*)

Reference	Parameters	Results		
		Overall	Mild	Moderate
Bosaeed, 2021[30]	Time to clinical recovery: normalization of temperature and respiratory symptoms, as well as the suppression of the cough, persisted for at least 72 h.	–	HR: 0.89, 95 % CI: 0.64–1.25 Median time FPV: 7 days (IQR: 4–11 days) Placebo + SoC: 7 days (IQR: 5–10 days)	–
Chuah, 2022[45]	Rate of clinical progression from nonhypoxia to hypoxia	RR:1.24, 95 % CI: 0.84–1.85 FPV: 18.40 % SoC: 14.80 %	RR: 1.38, 95 % CI: 0.71–2.67 FPV: 14.84 % SoC: 10.74 %	RR: 1.01, 95 % CI: 0.60–1.70 FPV: 18.85 % SoC: 18.60 %
Golan, 2022[43]	Time to sustained clinical recovery: based on oxygen saturation, oral temperature, and all COVID-19-associated symptoms for four consecutive days	Median time FPV: 7 days (95 % CI: 7–8 days) Control: 7 days (95 % CI: 6–8 days) Proportion: RR:1.01, 95 % CI: 0.96–1.05 F: 87.8 % SoC: 87.3 %		
Holubar, 2021[31]	Time to sustained symptom resolution: first of two consecutive days without symptoms.		HR: 0.87, 95 % CI: 0.52–1.45 Median time FPV: NA (95%CI: 26, NA) Placebo + SoC: 24 days (95%CI: 21, NA)	
Lou, 2021[41]	Time to an improvement of two points on a seven category the National Early Warning Score 2 (NEWS2) or live discharge from the hospital, whichever came first.			Median time FPV: 14 days (IQR: 6–38 days) Control: 15 days (IQR: 6–24 days) RR: 1.11, 95 % CI: 0.47–2.60 FPV: 55.55 % SoC: 50.00 %
McMahon, 2022[47]	Time to virological cure (two successive swabs negative for SARS-CoV-2 by PCR) Time to symptom resolution (fever, cough, sore throat, fatigue)	Time to virological cure: Log-rank p = 0.6 Fever: Log-rank p = 0.3 Cough: Log-rank p = 0.6 Sore throat: Log-rank p = 0.7 Fatigue: Log-rank p = 0.4		
Ruzhentsova, 2021[32]	Time to a reduction of patient clinical status on at least 1 score according to the WHO 8-Category Ordinal Scale compared to baseline.		HR: 1.60, 95 % CI: 0.78–3.26	
Shenoy, 2021[46]	Time to resolution of hypoxia: attainment of a score of four or lower on the WHO 10-point ordinal scale of clinical status			HR: 1.21, 95 % CI: 0.85–1.73 Median time FPV: 6 days Placebo: 7 days
Udwadia, 2021[34]	Time to clinical cure: according to clinician assessment and clinical parameters such as normalization of fever, respiratory rate, oxygen saturation as well as cough relief persisted for ≥72 h.		HR: 1.47, 95 % CI: 0.77–2.81 Median time FPV: 3 days (IQR: 2–4 days) Control: 4 days (IQR: 3–5 days) RR: 0.97, 95 % CI: 0.90–1.03 FPV: 96.55 % SoC: 100 %	

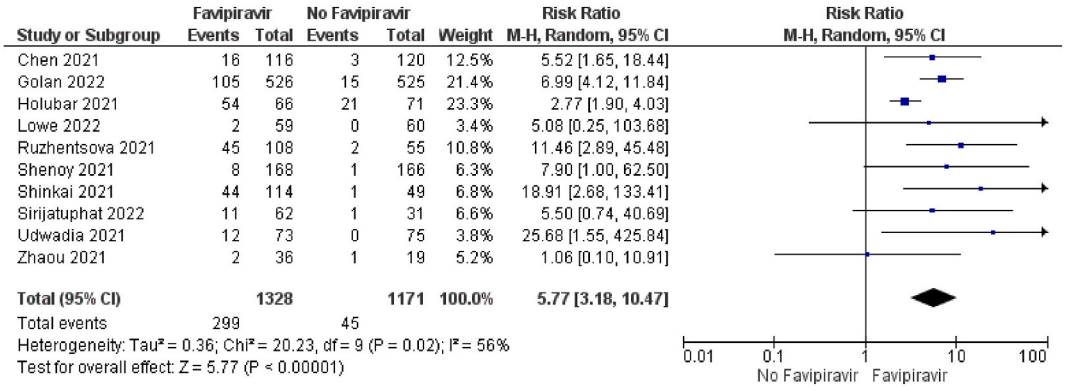

Fig. 5. The risk of hyperuricemia is higher in patients treated with favipiravir.

2.2. Search strategy

Papers reporting the results of randomized controlled trials published until January 6th, 2023, from PubMed, Embase, Web of Science, and Cochrane databases were systematically reviewed. The search queries for each database were developed by MAB with suggestions from DC and final checked by IYK, MM, and RB. The search strategy consists of two main keywords, "COVID-19" and "favipiravir". First, we built a systematic search strategy for the PubMed database by combining the keywords with medical subject headings [Mesh] terms, synonyms, and Boolean operators (AND, OR). The final query was then adjusted to the search strategy needed for other databases. We also did reference tracking from eligible articles and published systematic reviews and meta-analyses on favipiravir. Only full text artciles were considered. We applied no language restriction. The search results from all databases were sent to Rayyan (http://rayyan.qcri.org) to remove duplicate records and help the screening process. The complete search queries are available in the Supplementary material.

2.3. Record screening

The titles and abstracts of selected papers from each database were first screened by two independent reviewers (MAB and IYK). To reach a consensus, the conflicting screening results were discussed and the opinion of a third reviewer (DC) was sought. MAB and IYK then again screened the results by evaluating the full text independently to obtain the eligible studies. The disagreements were discussed, and the third reviewer's opinion was again asked to solve the discrepancies. We provide the level of inter-rater agreement for each step of the screening process using a percentage of agreement and Cohen's kappa (κ) statistic.

2.4. Data extraction

MAB and IYK extracted data independently using a data extraction form that had been pre-piloted. Data on the study characteristics (authors, year, country, study design), patient characteristics (number, age, sex), disease severity (mild or moderate), setting of care (inpatient or outpatient), drug information of intervention and comparator (dose, route of administration, duration), onset of symptoms to randomization, and parameters of efficacy and safety were extracted.

2.5. Study risk of bias assessment

The Cochrane risk-of-bias tool for randomized trials was used to assess the methodological quality of the included studies [9]. The appraisal of study quality was done by MAB and IYK separately. Disagreements between the two reviewers were resolved by discussion and the participation of the third reviewer (DC) was considered if no consensus was reached.

2.6. Statistical analysis

Time-to-event endpoints were measured with a hazard ratio (HR) and dichotomous endpoints were measured with a risk ratio (RR), with the exception of mortality, where – due to the zero risks – Risk Difference (RD) was used instead. Lowe et al. did not report HR on viral clearance but presented data (in its Supplementary Fig. 4) that made it possible to directly calculate HR under the assumption that patients who once had undetectable viral load will remain undetectable [10]. We provided a sensitivity analysis without the study by Lowe et al. in the Supplementary material (Fig. S1). All results are accompanied by a 95 % confidence interval (CI). A random-effects meta-analysis was used for the data analysis. The I^2 statistics and the standard χ^2 test were used to measure and detect statistical heterogeneity, respectively. The $I^2 > 50$ % and $p < 0.1$ indicated the presence of important heterogeneity [11]. Subgroup analyses were performed to identify the source of heterogeneity. Stratification based on the severity of the disease (mild/moderate) and the care

setting (inpatient/outpatient) on the primary outcome was performed in the subgroup analysis. Furthermore, a sensitivity analysis was also performed by excluding a study responsible for the statistical heterogeneity. A funnel plot and Egger's regression test were provided to detect publication bias for each main outcome. The Review Manager (RevMan) 5.4.1 software from Cochrane was used in this meta-analysis.

3. Results

3.1. Study selection

The systematic searching queries generated 883, 3334, 984, and 172 hits in PubMed, Embase, Web of Science, and Cochrane Library, respectively. After eliminating duplicate records (n = 1551), 3822 distinct entries were available for title and abstract (TIAB) screening. This first screening stage resulted in 49 eligible records that then entered the second stage of the screening process. The full-text assessment led to the exclusion of 29 articles for several reasons, such as retracted articles (n = 2), wrong study designs (n = 14), abstract proceeding (n = 3), favipiravir combined with another antiviral drug (n = 5), wrong comparison (n = 1), wrong severity (n = 3), and a parenteral administration (n = 1). Therefore, the final number of articles included was 20 (Fig. 1). For the TIAB screening, there was 99.5 % agreement between reviewers, with a kappa value of 0.71 (good). Meanwhile, the agreement rate for the entire text screening was 96.4 %, with a kappa value of 0.93 (very good).

3.2. Study characteristics

Among 20 articles, there were twelve open-label, seven double-blind, and one single-blind randomized controlled trial with mild to moderate COVID-19 severity. The location of the studies is quite diverse; there were four studies in Russia, three studies in China, and one study in Australia, Bahrain, Bangladesh, India, Iran, Japan, Kuwait, Malaysia, Saudi Arabia, Thailand, the UK, and the USA, respectively. There was one study that involved multiple countries, ie, Brazil, Mexico, and the USA. Based on the setting of patient care, there were 13 studies involving patients with inpatient care, five studies with patients attending outpatient care, and two with both types of patients. All studies used a loading dose of oral favipiravir on the first day of treatment with a range of doses between 1600, 1800 or 2200 mg two to three times a day. The dose of favipiravir on the second day of treatment until the end of the study (5–14 days) ranged from 1200 to 1800 mg daily, divided into two, three, or four doses. The duration from the onset of symptoms to the day of randomization was less than 12 days for most of the studies. The characteristics of each eligible article are presented in Table 1. Each study contains a variety of outcomes which are summarized in Supplementary material (Table S1).

3.3. Methodological assessments of articles

Of the 20 eligible articles, three studies did not provide detailed information on the randomization method and four did not mention whether the allocation of treatment to patients was concealed. Furthermore, there were twelve unblinded studies. The summary and graph of risk of bias can be found in Fig. 2 and Fig. S2, respectively.

3.4. Outcomes of meta-analysis

3.4.1. Primary efficacy outcomes

There were eight studies that reported the HR for viral clearence [10,12–18] (Supplementary material, Table S1). There were no statistically significant differences between the favipiravir and comparator groups in viral clearance (HR = 1.20 [95 % CI: 0.98–1.47, p = 0.09], I^2 = 40 %) (Fig. 3). The subgroup analysis by disease severity showed that favipiravir treatment significantly increased viral clearance by 59 % (HR = 1.59 [95 % CI: 1.25–2.03, p < 0.01], I^2 = 0 %) compared ot he comparators in patients with moderate severity of COVID-19 (Fig. 4). On the contrary, favipiravir had no significant effects on viral clearance (HR = 0.98 [95 % CI: 0.80–1.20, p = 0.85], I^2 = 0 %) in COVID-19 patients with mild symptoms (Fig. 4).

The results of subgroup analysis by healthcare settings indicated that the favipiravir group had significantly higher viral clearance (HR = 1.42 [95 % CI: 1.11–1.82, p < 0.01], I^2 = 20 %) in the inpatient care setting than in the comparator groups (Fig. S3). However, in the outpatient care setting, the comparable results for the viral clearance (HR = 1.01 [95 % CI: 0.77–1.33, p = 0.93], I^2 = 36 %) showed no significant effect of favipiravir (Fig. S3).

These results are also supported by the analysis of the proportion of patients who achieved viral clearance rather than the time to viral clearance. There were 13 studies that contained information on RR for viral clearance [10,12,13,15–17,19–25] (Table S1). Viral clearance was significantly higher in the groups treated with favipiravir with moderate severity (RR = 1.16 [95 % CI: 1.02–1.32, p < 0.01], I^2 = 0 %) and in those who were treated in the hospital (RR = 1.17 [95 % CI: 1.06–1.28, p < 0.01], I^2 = 18.9 %) than in the case of the comparators (Fig. S4a and Fig. S5a). This efficacy was not observed in the group treated with favipiravir with mild COVID-19 (RR = 1.01 [95 % CI: 0.95–1.07, p = 0.84], I^2 = 41.9 %) and in those who were treated in ambulatory care (RR = 1.04 [95 % CI: 0.92–1.17, p = 0.51], I^2 = 26.7 %) compared to the comparator groups (Fig. S4b and Fig. S5b).

3.4.2. Secondary efficacy outcomes

There were 16 studies that reported clinical improvement as an indicator to demonstrate the effectiveness of favipiravir. However, those studies used various parameters to define clinical improvements (Table 2). Seven studies indicated that favipiravir significantly

increased the likelihood of clinical recovery compared to the comparators. Among these studies, five studies demonstrated that favipiravir increased clinical cure in patients with COVID-19 with moderate symptoms significantly compared to the comparator groups [3,15,16,21]. There was only one study indicating that favipiravir significantly improved the clinical condition of COVID-19 patients with mild symptoms compared to the control group [18]. Another study did not have a subgroup analysis by severity [14,26].

Ten studies did not support that favipiravir was associated with a better clinical improvement than the comparators. Five studies provided evidence for patients with mild symptoms and three studies for patients with moderate symptoms [12,13,16,23,27,28]. There studies did not provide a subgroup analysis by severity [19,25,29].

All studies reported at least one of the other secondary outcomes that can be pooled in the meta-analysis (Table S1). The use of favipiravir was associated with a greater improvement in chest imaging (RR = 1.23 [95 % CI: 1.03–1.45, p = 0.02], I^2 = 20 %) than in the comparator group (Fig. S6a). There were no significant differences between the two groups for other outcomes such as mortality (RD = −0.00 [95 % CI: 0.01-0.00, p = 0.88], I^2 = 0 %), emergency department visits (RR = 1.15 [95 % CI: 0.50–2.66, p = 0.74], I^2 = 28 %), hospitalisations (RR = 1.05 [95 % CI: 0.54–2.05, p = 0.89], I^2 = 35 %), ICU (RR = 1.24 [95 % CI: 0.67–2.32, p = 0.49], I^2 = 0 %), and hospital discharge (RR = 1.09 [95 % CI: 0.96–1.24, p = 0.20], I^2 = 76 %) (Figs. S6b–g). The result for hospital discharge had substantial heterogeneity. Therefore, we performed a sensitivity analysis excluding one study, which decreased heterogeneity; however, the difference was still not significant (RR = 1.04 [95 % CI 0.97–1.12, p = 0.23], I^2 = 14 %) (Fig. S6g).

3.4.3. Safety outcomes

17 studies reported at least one side effect that can be analysed in the meta-analysis [3,10,12–20,23–26,28,29] (Table S1). The risks of developing low haemoglobin, hyperglycemia, elevated ALT and AST, high bilirubin, elevated creatine phosphokinase, high triglycerides, and leukopenia were comparable between the favipiravir and comparator groups (Fig. S7). Furthermore, the risks that both groups would experience other symptoms, such as abdominal pain, anorexia, constipation, diarrhea, dizziness, dyspnea, headache, myalgia, nasal congestion, nausea, rhinorrhoea, skin rash and vomiting, were also not significantly different (Fig. S8). It is noteworthy that the frequency of these symptoms might be influenced by the disease itself. However, a meta-analysis of ten studies indicated that patients treated with favipiravir were almost six times more likely to develop hyperuricemia than those who did not receive favipiravir (RR = 5.77 [95 % CI 3.18–10.47, p < 0.01], I^2 = 56 %) (Fig. 5) [3,10,13–18,25,28]. Since heterogeneity was moderate, we performed a sensitivity analysis excluding a study by Holubar et al. (2021) [13]. The result indicated that the favipiravir regimen increased the risk of hyperuricemia more than seven times (RR = 7.12 [95 % CI: 4.73–10.72, p < 0.01], I^2 = 0 %) compared to the comparator treatment. (Fig. S9). In general, favipiravir can be considered a safe drug since the incidence of adverse events observed in the favipiravir group was not significantly different from the comparator group, except for the risk of hyperuricemia.

3.5. Publication bias

The funnel plots for the primary outcome (viral clearance) and the safety outcome (hyperuricemia) were presented in the Supplementary material (Figs. S10a–b). The Egger's regression test results (p > 0.05) indicated no publication bias for the outcomes. However, the Cochrane handbook recommended not to use the funnel plot and Egger's regression test if the number of studies included in the meta-analysis of the outcomes is less than ten studies since the test would have a low power to detect the real asymmetry [9]. In our analysis, the number of included studies for viral clarance is below ten.

4. Discussion

Favipiravir has been used in many countries to treat COVID-19 infections shortly after the outbreak of the pandemic [5,6]. Although this was an off-label application, the lack of drugs with proven efficacy required the use of repurposed drugs, the efficacy of which could be based mainly on preclinical data. The efficacy of favipiravir has been studied in several clinical trials since its introduction into COVID-19 therapy [3,4]. The results of these trials have been summarized in meta-analyses. The findings of these meta-analyses do not allow a definitive conclusion to be drawn on the efficacy of favipiravir. This could be attributable in part to the diversity of study populations, interventions, comparators, and results. The first meta-analysis was published in September 2020. Altogether, four studies were included in the quantitative synthesis, one of which was not randomized. There was a statistically significant clinical improvement in the favipiravir group on day 14 compared to other antivirals or standard of care (RR = 1.29, 95 % CI 1.08–1.54). No significant differences were observed between the two groups in non-invasive ventilation or oxygen requirement (OR = 0.76, 95 % CI: 0.42–1.39), viral clearance (day 14: RR = 1.06, 95 % CI: 0.84–1.33), and adverse effects (OR = 0.69, 95 % CI: 0.13–3.57) [30].

The most recent meta-analysis evaluated the efficacy and adverse effects of favipiravir based on randomized clinical trials, observational studies, case series, and case reports. Overall, 157 studies (the majority of which were case reports) were included. Favipiravir showed a higher rate of viral clearance on day 5 (RR = 1.60, p = 0.02) in hospitalized patients compared to standard of care. A similar finding was made for chest radiological improvement (RR = 1.33, p < 0.01), normalization of body temperature on days 3–4 (RR = 1.99, p < 0.01), hospital discharge on days 10–11 (RR = 1.19, p < 0.01), and shorter clinical improvement time (MD = −1.18, p = 0.05). In patients treated with favipiravir, the risk of hyperuricemia was higher (RR = 9.42, p < 0.01), as was the increase in alanine aminotransferase (RR = 1.35, p < 0.01). There were no differences in the increase in aspartate aminotransferase level (RR = 1.11, p = 0.25). Nausea (RR = 0.42, p < 0.01) and vomiting (RR = 0.19, p = 0.02) was less frequent in the favipiravir group. There were no differences in mortality (RR = 1.19, p = 0.32). In the case of non-hospitalized patients, no significant differences were reported [31].

Our meta-analysis is the first meta-analysis of randomized controlled trials that assesses the efficacy of favipiravir in viral clearance time as the primary outcome measure. Since no significant differences in viral clearance rate (HR = 1.20 [95 % CI: 0.98–1.47, p = 0.09], $I^2 = 40$ %) could be detected compared to comparator treatment, the use of favipiravir as first choice treatment is questionable. Its beneficial effects could only be confirmed in patients with moderate symptoms (59 % significant increase in the rate of viral clearance (HR = 1.59 [95 % CI: 1.25–2.03, p < 0.01], $I^2 = 0$ %)), however, this finding does not support the use of favipiravir as routine therapy that should be started after the diagnosis of COVID-19. No beneficial effect was observed in those with mild symptoms. According to previous data, favipiravir significantly increased the risk of hyperuricemia (RR = 5.77 [95 % CI: 3.18–10.47, p < 0.01], $I^2 =$ 56 %) compared to the comparator group, which should be considered when making therapeutic decisions.

The main strength of our trial is that the meta-analysis is based only on the results of randomized, controlled trials. The 20 included trials were carried out by independent research groups in different countries in Europe, America, Asia, and Australia. However, our study has several limitations that require special caution when interpreting the results. Although the studies were randomized, many of them were open-label trials. Study populations may be heterogeneous in several aspects and the measure of heterogeneity is predominantly unknown due to inadequate reporting. First, the included trials were published between 2020 and 2022, when COVID-19 was caused by different variants of SARS-CoV-2; however, most of the trials did not include the identification of virus variants. Second, the grading of clinical severity (which has influence on hospitalization as well) may differ in different countries and hospitals, and the criteria by which grading was performed was not available in the studies. Third, standard-of-care therapies might be diverse geographically and in time - unfortunately, the exact therapeutic protocols were mostly not disclosed in the individual studies. Fourth, younger adults are over-represented in the majority of the trials; moreover, the exact age distribution could not be determined based on the available data. Fifth, although it is known that favipiravir is more effective in the first phase of the disease, in some trials randomization was performed within 10–12 days of the onset of initial symptoms. Sixth, the vaccination status of the patients was unclear. And finally, some applied methods (PCR analysis, temperature measurement) were not described in the studies, which may also be a source of heterogeneity. However, from the point of view of rational pharmacology, these limitations do not undermine the principal conclusion of our study, which is that the use of favipiravir in mild to moderate COVID-19 is not justified by available data.

5. Conclusions

Favipiravir treatment did not have a significant effect on the viral clearance rate compared to comparator treatment. Its efficacy could be demonstrated in a subgroup analysis of patients with moderate severity COVID-19, however, favipiravir had no significant effects on viral clearance in patients with COVID-19 with mild symptoms and treated in ambulatory care. Based on these results, the use of favipiravir as a routine therapy that should be initialized after the diagnosis of COVID-19 is questionable.

Ethics statement

Review and/or approval by an ethics committee was not needed for this study because as a systematic review article does not require ethical approval. Our systematic review and meta-analysis protocol was registered with PROSPERO (registration number CRD4202232443).

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this research is a meta-analysis of already publisjhed data.

Data availability statement

All the data that are the basis of this study can be found in the article or the supplementary material.

CRediT authorship contribution statement

Muh Akbar Bahar: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ikhwan Yuda Kusuma:** Writing – original draft, Methodology, Investigation, Formal analysis. **Ádám Visnyovszki:** Writing – review & editing. **Mária Matuz:** Writing – review & editing. **Ria Benkő:** Writing – review & editing. **Tamás Ferenci:** Writing – review & editing, Methodology. **Bálint Gergely Szabó:** Writing – review & editing. **Edit Hajdú:** Writing – review & editing. **Zoltán Pető:** Writing – review & editing. **Dezső Csupor:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Writefull in order to improve language. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29808.

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