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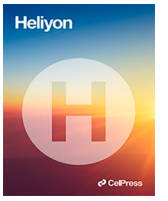

Research article

Ivermectin for treatment of COVID-19: A systematic review and meta-analysis

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ABSTRACT

The effect of ivermectin (IVM) in treating coronavirus disease 2019 (COVID-19) is still controversial, yet the drug has been widely used in the world. The aim of this review was to systematically evaluate the clinical outcomes of IVM in patients with COVID-19. From inception to June 22, 2023, the PubMed, EMBASE, Web of Science (WOS), and scopus databases were searched for relevant observational studies on the risk of RA in migraineurs. We searched PubMed/Medline, EMBASE, the Cochrane Library, Web of Science, medRxiv, and bioRxiv to collect all relevant publications from inception to June 22, 2023. Primary outcomes were all-cause mortality rate, mechanical ventilation (MV) requirement, PCR negative conversion, and adverse events (AEs). Revman 5.4 was used to assess the risk of bias (RoB) and quality of evidence. Thirty-three RCTs (n = 10,489) were included. No significant difference in all-cause mortality rates or PCR negative conversion between IVM and controls. There were significant differences in MV requirement (RR 0.67, 95% CI 0.47–0.96) and AEs (RR 0.87, 95% CI 0.80–0.95) between the two groups. Ivermectin could reduce the risk of MV requirement and AEs in patients with COVID-19, without increasing other risks. In the absence of a better alternative, clinicians could use it with caution.

1. Introduction

Despite the concerted efforts and the relatively successful vaccination against the coronavirus disease 2019 (COVID-19) around the world [1,2], the pandemic is likely to last for a long time due to the emergence of multiple variants and anti-vaccine movements worldwide [3–5]. In this context, the potential of several drugs to alleviate the symptoms of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or the symptoms of COVID-19 has been evaluated [6]. However, to date, few pharmacotherapies have shown efficacy in reducing the rate of hospitalizations, mortality, or mechanical ventilation (MV) [7,8].

Drug repositioning, also known as drug recycling or drug repurposing, is an effective approach to find new indications for approved drug. A repositioned drug has all reliable data of safety and pharmacokinetic profiling [9,10]. Therefore, drug repositioning is highly efficient, low-cost and riskless. Which can significantly reduce the time required to produce an effective drug to treat COVID-19. Ivermectin (IVM), a semisynthetic, anti-parasite agent [11], has attracted much attention as a potential drug for COVID-19 [12], and has been widely used off label to control COVID-19 [13–15]. In cells infected by SARS-CoV-2, IVM has been shown to inhibit both viral adherence and replication, and can reduce the concentration of viral RNA by nearly 5000-fold [16–18]. Which raised hopes of

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clinical benefit to the treatment of COVID-19. However, the concentration in cell culture was equivalent to >50-fold the normal maximum safe dosage allowed for patients daily, which raised concerns about the efficacious dose and tolerability of ivermectin for the treatment of SARS-CoV-2 infection in humans [18].

Multiple clinical trials have been conducted to evaluate clinical outcomes [19–26], with contradictory outcomes, and some of these studies have been withdrawn or retracted for fear of serious data inconsistencies or research fraud [27–29]. It is imperative to synthesize evidence for clinicians and communities. Systematic reviews have been performed on this topic, but in the majority of them a retracted trial accounted for more than 10% of the overall effect [27,30–32], which overestimated the benefits. However, we additionally evaluated hospital admission, mortality, arrhythmia, and compliance. In addition, we enrolled more studies, and the sample size was larger.

Because the available evidence on the benefits of IVM in the treatment of people with COVID-19 remains controversial and there is a risk of serious adverse events (SAEs), the WHO living guideline recommends IVM for COVID-19 only within clinical trials, and the Infectious Diseases Society of America's guideline suggests against IVM for treating patients with COVID-19 [6,33]. Therefore, there is still a lack of up-to-date and reliable evidence synthesis of the effect of IVM in patients with COVID-19. The aim of this study was to synthesize the evidence to critically appraise the therapeutic effects and adverse events (AEs) of IVM for COVID-19.

2. Method

This systematic review was carried out based on recommendations from the Cochrane Handbook [34] and the latest Preferred Reporting Items for Systematic Reviews of Interventions (PRISMA 2020) statements [35], and the protocol of our study was prospectively registered in PROSPERO (CRD42022364559).

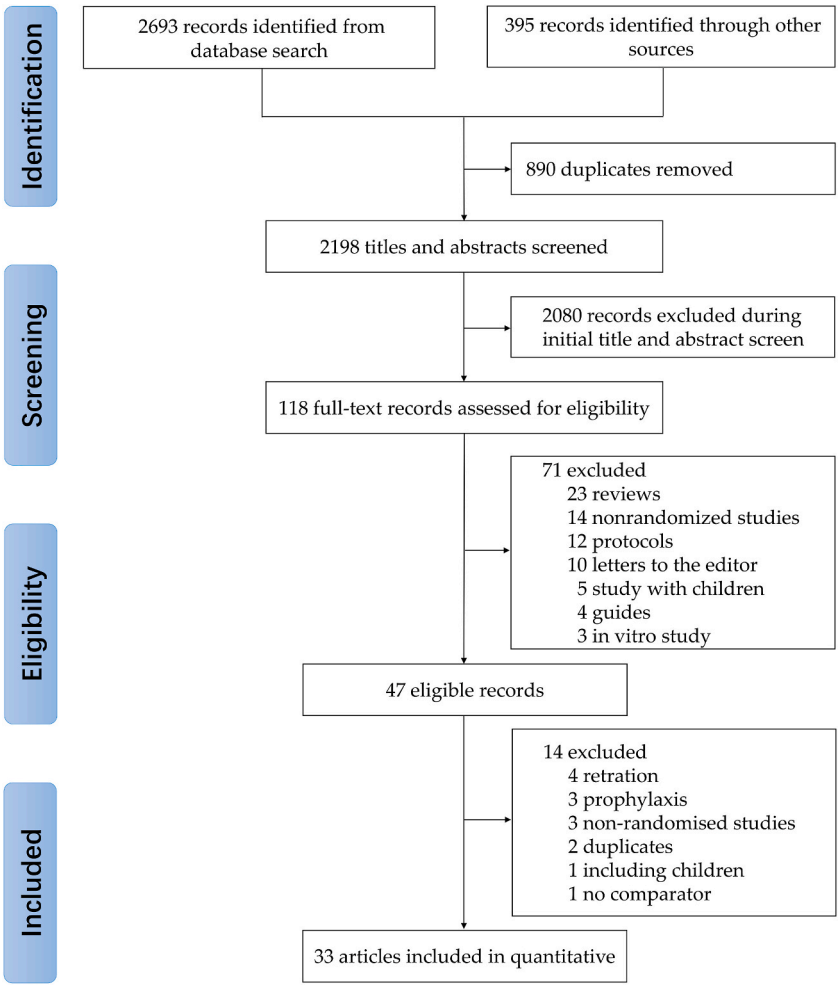

Fig. 1. PRISMA flow diagram.

2.1. Search strategy

We searched PubMed/Medline, EMBASE, the Cochrane Library, Web of Science, medRxiv, and bioRxiv to collect all relevant publications from inception to June 22, 2023. There were no restrictions on language, publication status, date, region, or participant demographics. Descriptors were identified in Medical Subject Headings (MeSH), Embase Subject Headings (Emtree) and *Descritores em Ciências da Saúde* (Decs). The Cochrane-validated filter for randomized controlled trials was used [36]. The search strategy was adjusted based on descriptors in each specific database and the complete search strategy is shown in Fig. 1. In addition, references of all included studies were also searched manually to identify any potential qualified studies.

2.2. Eligibility criteria

We included randomized controlled trials (RCTs) reporting benefit or harm outcomes of IVM for treating adults with COVID-19, irrespective of COVID-19 severity. Controls were placebo or the standard of care (SOC). Case reports, case series, policy reports, conference abstracts, commentaries, and editorials were excluded. Studies evaluated the use of IVM as adjuvant or combination therapy were excluded. Studies assessing IVM as prophylaxis against COVID-19 infection were also excluded.

2.3. Outcomes

Primary outcomes were all-cause mortality rate, length of hospital stay (LOS), PCR negative conversion, and AEs; and secondary outcomes included symptoms resolved, viral clearance, admission to intensive care unit (ICU), MV requirement, discharged from hospital, hospitalization due to progression, and SAEs. AEs were defined based on Common Terminology Criteria for Adverse Events (CTCAE), and SAEs were defined based on Food and Drug Administration (FDA) and National Cancer Institute (NCI).

2.4. Data extraction

Two investigators (ZS and SS) independently screened titles and abstracts, and then evaluated full texts of selected abstracts. Disagreements were resolved through discussion or by a third investigator (YZ).

We developed a Microsoft Excel template to extract data systematically, including study design (methods, location, eligible criteria, follow-up duration and sample size), participant characteristics (disease severity, sex and age), intervention and comparator characteristics (dosage and frequency of IVM/comparator, comparator, outcome measures at baseline, and measures of outcome from baseline to the end of follow-up). In studies with more than two study arms, only data from arms relevant to our review were extracted.

We planned to contact authors of (potentially) eligible studies to provide relevant information. If a study reported interquartile range and median, methods recommended by Wan et al. [37] and Luo et al. [38] were used to estimate the standard deviation (SD) and mean deviation (MD) for data pooling if there were no significant bias on the ground of the test by Shi et al. [39].

2.5. Quality assessment

Two authors (ZS and LZ) independently evaluated trials for risk of bias using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) [40]. The overall certainty of the body of evidence was rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, allowing for overall risk of bias, consistency of effect, imprecision, indirectness and publication bias to assess the certainty of the body of evidence [41,42]. In case of serious concerns in any of these domains, the quality of evidence will be rated down. The overall RoB 2.0 judgment was incorporated into the GRADE assessment.

2.6. Statistical synthesis

LOS was expressed as mean difference; for other outcomes, we pooled RR and its 95% confidence interval (CI) using a fixed-effects or random-effects model depending on the presence of heterogeneity [43,44]. Heterogeneity between studies was assessed using Cochran's Q test with a significance level of $P < 0.10$ and further quantified using I^2 statistics. When values were less than 25%, 25–75%, and more than 75%, respectively, I^2 values were rated as low, moderate, and high degrees of heterogeneity.

Subgroup analysis was conducted for all-cause mortality rate by the controls, and sensitivity analysis was conducted for all-cause mortality rate by severity of COVID-19.

Funnel plot was drawn to investigate the possibility of publication bias, and the symmetry of the funnel plot was visually evaluated [45].

Analyses were performed using the RevMan 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020).

3. Results

3.1. Literature selection and study characteristics

Through a systematic database search, we identified 2693 records and 395 additional records from the gray literature. 118 full-text articles or unpublished datasets were evaluated for eligibility after the removal of 890 duplicates and 2198 at title and abstract review

Table 1
Characteristics of studies entered into meta-analysis.

Study Authors (Year)	Name of publication	Country (Sample Size)	IVM Dose and Duration	ControlGroup	COVID-19 Severity by WHO Classification	Patient Age, Mean (SD) or Median (IQR), y	Patients, %						Evaluated outcomes	Duration of Follow-up, d	Funding
							Laboratory-confirmed COVID-19	Hospitalized	Female Sex	CVD or CHD	DM	HTN			
Abbas et al. (2022) [63]	Indian J. Pharm. Sci.	China (n = 202)	300 μg/kg per day for 5 days	Placebo	Mild in 100%	IVM: 38.33 (6.84) Control: 37.33 (5.84)	100	100	55.4	0	0	0	All-cause mortality rate, Symptoms resolved, SAEs, Hospitalization due to progression	21	ND
Abd-Elsalam et al. (2021) [65]	J. Med. Virol.	Egypt (n = 164)	12 mg (single dose) for 3 days + SOC	SOC	Mild to moderate	IVM: 42.38 (16.02) Control: 39.38 (16.92)	100	100	50	ND	16.5	19.5	MV requirement, All-cause mortality rate, LOS	30	ND
Ahmed et al. (2021) [61]	Int. J. Infect. Dis.	Bangladesh (n = 48)	12 mg once daily for 5 d	Placebo	Mild in 100%	42 (NR)	100	100	54	0	0	0	Remission of symptoms, LOS, SAEs, Oxygen requirement, Time to viral clearance	14	Industry
Angkasekwinai et al. (2022) [80]	Antibiotics	Thailand (n = 447)	400–600 μg/kg, once daily for 2 days	Placebo	Mild in 11.6%, moderate in 88.4%	39.5 (12.1)	100	7.4	56.8	1.8	6.9	11.2	All-cause mortality rate, AEs, Symptoms resolved, SAEs,	28	Government
Aref et al. (2021) [66]	Int. J. Nanomed.	Egypt (n = 114)	spray twice daily + SOC	SOC	Mild in 100%	45.1 (18.9)	100	0	28.1	3.5	12.3	17.5	PCR negative conversion, Progress to more severe disease, Duration taken for negative, AEs	18	Government
Babalola et al. (2022) [76]	QJM	Nigeria (n = 62)	given every 84 h, twice a week for 2 weeks + SOC: A1: 6 mg; A2: 12 mg	Placebo + SOC	Asymptomatic or mild/ moderate symptoms	44.1 (14.7)	100	ND	30.6	ND	3.2	14.5	All-cause mortality rate, Duration taken for negative, AEs, SAEs	42	ND
Beltrán-Gonzalez et al. (2022) [74]	Infect. Dis. Rep.	Mexico (n = 106)	12 mg or 18 mg, according to patient weight	Placebo	Severe in 100%	53 (16.9)	100	100	37.8	ND	33.9	32.1	All-cause mortality rate, clinical recovery, LOS, AEs, Respiratory deterioration	28	Government
Biber et al. (2022) [72]	Int. J. Infect. Dis.	Israel (=89)	Ivermectin 0.2 mg/kg for 3 days	Placebo	Mild to moderate, not requiring O_2 and	35 (28–47) (IQR)	100	0	21.3	ND	ND	ND	PCR negative conversion, AEs, Hospitalization due to	21	ND

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Table 1 (*continued*)

Study Authors (Year)	Name of publication	Country (Sample Size)	IVM Dose and Duration	ControlGroup	COVID-19 Severity by WHO Classification	Patient Age, Mean (SD) or Median (IQR), y	Patients, %						Evaluated outcomes	Duration of Follow-up, d	Funding
							Laboratory-confirmed COVID-19	Hospitalized	Female Sex	CVD or CHD	DM	HTN			
					asymptomatic cases								progression, SAEs		
Bramante et al. (2022) [21]	New Engl. J. Med.	USA (n = 1323)	390–470 μg/kg per day, for 3 days	Placebo	Mild in 100%	46 ([IQR] 37–55)	100	0	56	22.8	1.6	ND	Hypoxemia, emergency department visit, Hospitalization, mortality	14	ND
Bukhari et al. (2021) [77]	Medrxiv	Pakistan (n = 86)	Single dose: 12 mg	SOC	Mild in most patients (percentage unclear)	39 (42)	100	100	15	5.8	12	14	Time to viral clearance, AEs	28	ND
Buonfrate et al. (2022) [22]	Int. J. AG.	Italy (n = 93)	Single dose A1: 600 μg/kg; A2: 1200 μg/kg	Placebo	Mild in 83.9%, moderate in 16.1%	47 (31–58)	100	100	41.9	23.4	4.7	ND	Viral clearance, Hospitalization due to progression, Mean durations of symptoms, Mean reduction in viral load, SAEs	14	Government
Chaccour et al. (2021) [79]	EClinicalMedicine	Spain (n = 24)	Single dose 400 μg/kg	Placebo	Mild in 100%	26 (19–36)	100	0	50	0	0	0	All-cause mortality rate, AEs, PCR at d 7	28	Government
Chachar et al. (2020) [78]	Int. J. Sci.	Pakistan (n = 50)	12 mg, 12 mg at 12 h, and 12 mg at 24 h	SOC	Mild in 100%	42 (16)	100	0	38	8	40	26	Asymptomatic at d 7	7	ND
Chahla et al. (2021) [58]	medRxiv	Argentina (n = 172)	24 mg every 7 days for 4 weeks + SOC	SOC	Mild in 100%	IVM: 40 (19–53) Placebo: 37.5 (31,49) IQR	100	0	52.3	ND	6.4	11	Symptoms resolved, Discharged from hospital	28	Government
Elshafie et al. (2022) [23]	Expert Rev. Anti. Infect. Ther.	Egypt (n = 206)	36 mg on day 1, 3, 6	Placebo	moderate to severe	59 (16)	35.4	100	46.6	9.7	27.7	38.3	All-cause mortality rate, AEs, Time or number of recovery	90	ND
Kishoria et al. (2020) [67]	Indian J. Res.	India (n = 32)	12 mg + SOC	SOC	Asymptomatic/ Mild patients in 100%	38	100	100	28.1	ND	ND	ND	PCR negative conversion, Discharged from hospital	6	ND
Krolewiecki et al. (2021) [59]	EClinicalMedicine	Argentina (n = 45)	0.6 mg/kg once daily for 5 d	SOC	Mild in 87%, moderate in 13%	41 (12)	100	100	44	ND	16	13	Viral load at d 5, IVM plasma level	30	Government

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Table 1 (*continued*)

Study Authors (Year)	Name of publication	Country (Sample Size)	IVM Dose and Duration	ControlGroup	COVID-19 Severity by WHO Classification	Patient Age, Mean (SD) or Median (IQR), y	Patients, %						Evaluated outcomes	Duration of Follow-up, d	Funding
							Laboratory-confirmed COVID-19	Hospitalized	Female Sex	CVD or CHD	DM	HTN			
Lim et al. (2022) [24]	JAMA Intern. Med.	Malaysia (n = 490)	0.4 mg/kg body weight daily for 5 days + SOC	SOC	Mild in 34.1%, moderate in 65.9%	62.5 (8.7)	100	0	54.5	11.6	53.5	75.3	All-cause mortality rate, LOS, Symptoms resolved, Admission to ICU, MV requirement, Progress to more severe disease	28	ND
López-Medina et al. (2021) [64]	JAMA	Colombia (n = 398)	300 μg/kg once daily for 5 d	Placebo	Mild in 100%	37 (29–48)	100	1	78	1.7	6	13	All-cause mortality rate, Time to complete resolution, AEs, SAEs, Escalation of care	21	Government
Manomaipiboon et al. (2022) [25]	Trials	Thailand (n = 72)	12 mg per day, for 5 days	SOC	Mild to moderate	48.57 (14.8)	100	100	62.5	2.8	23.6	40.3	PCR negative conversion, Symptoms resolved, Mean durations of symptoms	28	Government
Mirahmadizadeh et al. (2022) [26]	Respirology	Iran (n = 391)	3 mg for 2 days, cumulative dose of 24 mg	Placebo	Mild in 100%	39 (17)	100	0	49	1.1	5	6.9	All-cause mortality rate, Symptoms resolved, MV requirement, Hospitalization due to progression, AEs, SAEs, Mean durations of symptoms		Government
Mohan et al. (2021) [68]	J. Infect. Themother.	India (n = 157)	A1: Ivermectin 12 mg (single dose); A2: Ivermectin 24 mg (single dose)	Placebo	Mild in 64%, moderate in 36%	35.3 (10.4)	100	100	11.2	0.8	8.8	11.2	PCR negative conversion, Progress to more severe disease, Discharged from hospital, AEs, SAEs	14	Government
Naggie et al. (2022) [82]	JAMA	USA (n = 1591)	Ivermectin 400 μg/kg for 3 days	Placebo	Mild-to-moderate	48 (12)	100	0	59	ND	11.5	26	All-cause mortality rate, Admission to ICU, MV requirement,	28	Government

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Table 1 (*continued*)

Study Authors (Year)	Name of publication	Country (Sample Size)	IVM Dose and Duration	ControlGroup	COVID-19 Severity by WHO Classification	Patient Age, Mean (SD) or Median (IQR), y	Patients, %						Evaluated outcomes	Duration of Follow-up, d	Funding
							Laboratory-confirmed COVID-19	Hospitalized	Female Sex	CVD or CHD	DM	HTN			
													Hospitalization due to progression, Mean durations of symptoms, AEs, SAEs		
Naggie et al. (2023) [83]	JAMA	USA (n = 1206)	Ivermectin 600 μg/kg for 6 days	Placebo	Mild-to-moderate	IVM: 47 (38–58) Control:48 (39–58)	100	0	59.1	3.9	9	26.3	Time to sustained recovery, All-cause hospitalization rate, All-cause mortality rate	28	Government
Okumuş et al. (2021) [81]	BMC Infect. Dis.	Turkey (n = 60)	0.2 mg/kg for 5 days + SOC	SOC	Severe pneumonia	IVM: 58.17 (11.52) Control: 66.23 (13.31)	100	100	33.3	23.3	31.6	45	All-cause mortality rate, PCR negative conversion, Clinical improvement, AEs, SAEs	5	Government
Podder et al. (2020) [62]	IMC J. Med. Sci.	Bangladesh (n = 62)	Single dose: 200 μg/kg	SOC	Mild in 81%, moderate in 19%	39 (12)	100	ND	29	ND	ND	ND	Time to full recovery, Viral clearance	10	Government
Ravikirti et al. (2021) [69]	J. Pharm. Sci.	India (n = 115)	12 mg/d for 2 days	Placebo	Mild in 79%, moderate in 21%	53 (15)	100	100	28	11	36	35	All-cause mortality rate, Admission to ICU, MV requirement, Viral clearance at d 6	10	ND
Reis et al. (2022) [10]	New Engl. J. Med.	Brazil (n = 679)	Ivermectin: 400 μg per kilogram of body weight once daily for 3 days + SOC	Placebo + SOC	Mild-to-moderate	49 (38–57)	100	0	58.2	1.8	12.9	8.4	MV requirement, AEs, Hospitalization due to progression, Viral clearance	21	Government
Rezai et al. (2022) [70]	Front. Med.	Iran (n = 1158)	0.4 mg/kg per day for 3 days + SOC	Placebo + SOC	Moderate in 53.9%, severe in 46.1%	44.9 (5–96)	100	52.6	50	7.7	20.1	18.7	Clinical improvement, Recovery, LOS, ICU admission, MV requirement, AEs, Mortality	7	ND

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Table 1 (*continued*)

Study Authors (Year)	Name of publication	Country (Sample Size)	IVM Dose and Duration	ControlGroup	COVID-19 Severity by WHO Classification	Patient Age, Mean (SD) or Median (IQR), y	Patients, %						Evaluated outcomes	Duration of Follow-up, d	Funding
							Laboratory-confirmed COVID-19	Hospitalized	Female Sex	CVD or CHD	DM	HTN			
Rocha et al. (2022) [75]	BMC Infect. Dis.	Mexico (n = 56)	12 mg per day for 3 days + SOC	Placebo + SOC	asymptomatic and mild	IVM: 40.4 (15.2) Control:36.4 (13)	100	100	67.8	3/30: 1/26	2/30: 1/26	4/30 1/26	PCR negative conversion, Symptoms resolved, Progress to more severe disease, AEs	14	Industry
Shahbaznejad et al. (2021) [71]	Clin. Ther.	Iran (n = 69)	0.2 mg/kg + SOC	SOC	Moderate in 55%, severe in 45%	46.4 (22.5)	64	100	47.8	ND	ND	ND	Duration of hospital stay, Overall clinical improvement	10	ND
Vallejos et al. (2021) [60]	BMC Infect. Dis.	Argentina (n = 501)	IVM: BW < 80 kg: 12 mg at inclusion and another 12 mg after 24 h; 80 kg < BW < 110 kg:18 mg at inclusion and another 18 mg after 24 h; 110 kg < BW: 24 mg at inclusion and another 24 mg after 24 h + SOC	Placebo + SOC	Mild in 100%	42.5 (15.5)	100	0	47.3	2.6	9.6	23.6	All-cause mortality rate, PCR negative conversion, MV requirement, Hospitalization due to progression, AEs, SAEs	30	ND
Wada et al. (2023) [73]	Front. Med.	Japan (n = 221)	200 μg/kg	Placebo	Asymptomatic or mild/ moderate symptoms	47.7 (15.0)	100	0	35.4	ND	13.7	ND	Time to a negative, All-cause mortality rate, MV requirement, Hospitalization due to progression, AEs	45	Government

AEs: adverse events, CHD: coronary heart disease, CVD: cerebrovascular disease, DM: diabetes mellitus, HTN: hypertension, ICU: Intensive Care Unit, IVM: ivermectin, LOS: length of hospital stay, MV: mechanical ventilation, ND: No data available, PCR: polymerase chain reaction, SAEs: severe adverse events, SD: standard deviation, SOC: standards of care, IQR: interquartile range.

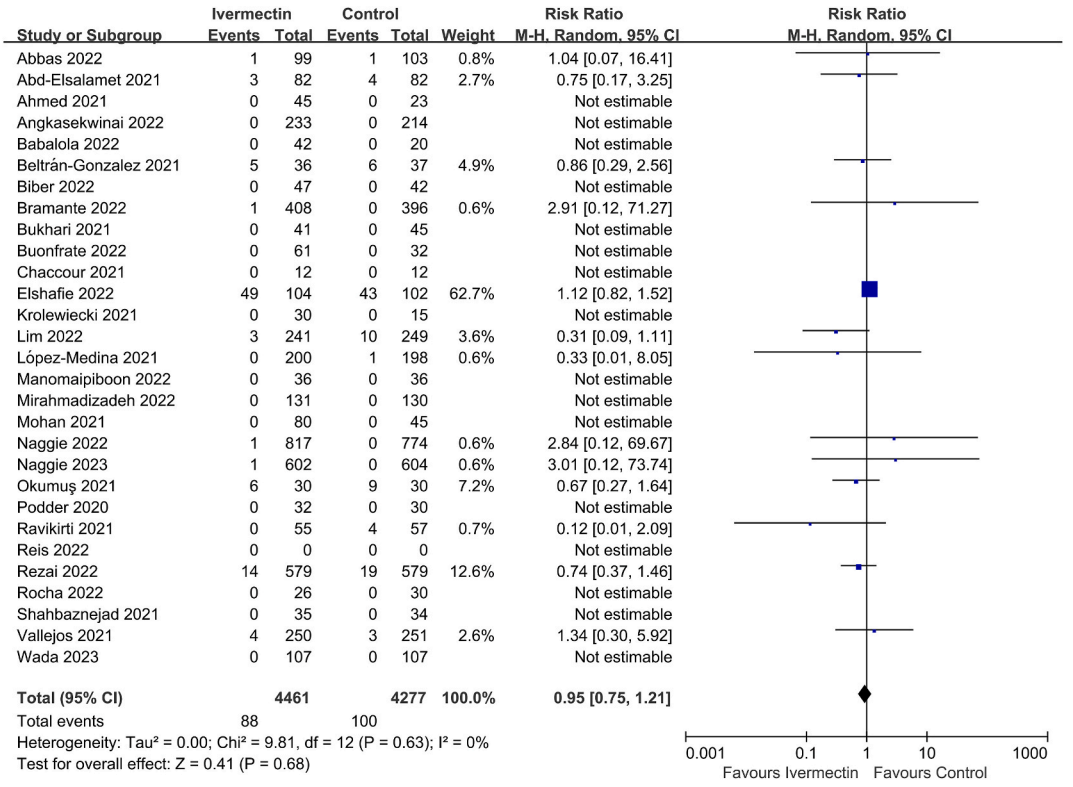

Fig. 2. Effect of ivermectin on all-cause mortality rates in patients with COVID-19.

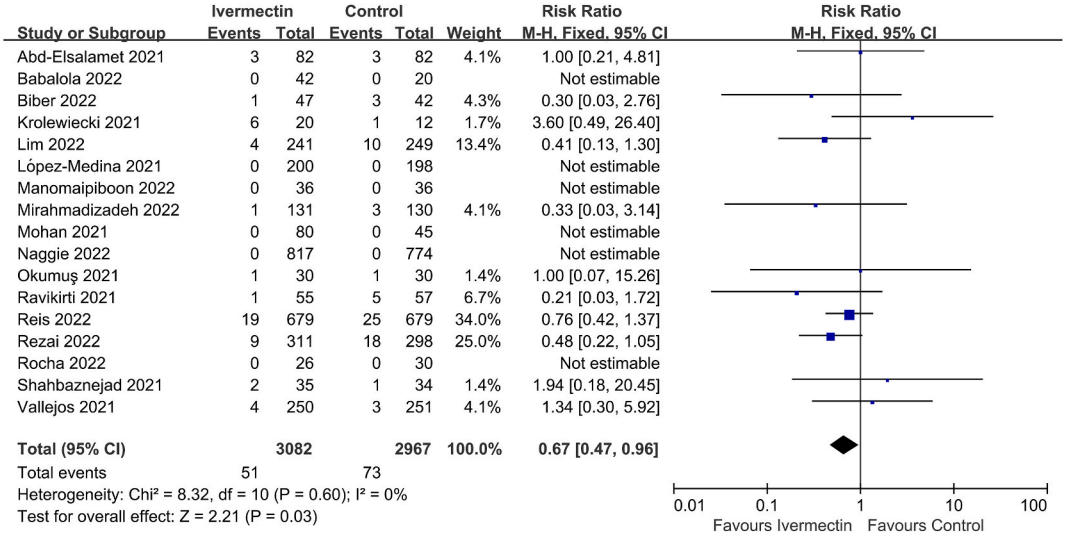

Fig. 3. Effect of ivermectin on mechanical ventilation requirement in patients with COVID-19.

stages. Full-text articles for the remaining 47 records were retrieved, of which three were excluded for evaluating IVM for COVID-19 prophylaxis [46–48], four due to retraction [28,29,49,50], three for the study design (not RCT) [51–53], two for duplicates [54,55], one due to including children [56], and one for no control group [57]. No additional studies were retrieved from reference lists of the enrolled studies. Therefore, 33 studies were qualified and included in our systematic review (Fig. 1).

Table 1 summarized the main characteristics of the included studies. COVID-19 disease severity was asymptomatic/mild in 12 randomized controlled trials, moderate in 1, mild and moderate in 17, severe in 2, and moderate and severe in 1. Studies were done in 19 countries: Argentina (n = 3 studies) [58–60], Bangladesh (n = 2) [61,62], Brazil (n = 1) [10], China (n = 1) [63], Colombia (n = 1)

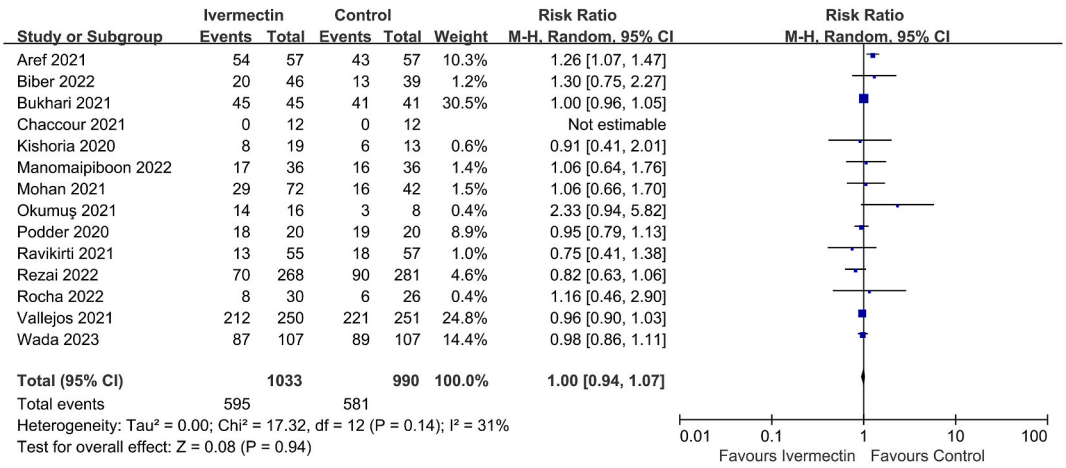

Fig. 4. Effect of ivermectin on PCR negative conversion in patients with COVID-19.

[64], Egypt (n = 3) [23,65,66], India (n = 3) [67–69], Iran (n = 3) [26,70,71], Israel (n = 1) [72], Italy (n = 1) [22], Japan, (n = 1) [73], Malaysia (n = 1) [24], Mexico (n = 2) [74,75], Nigeria (n = 1) [76], Pakistan (n = 2) [77,78], Spain (n = 1) [79], Thailand (n = 2) [25,80], Turkey (n = 1) [81], and USA (n = 3) [21,82,83]. Of all 33 studies, 7 had an overall high risk of bias, 13 had some concerns of bias, and 13 had a low risk (Supplementary Fig. 1).

3.2. Meta-analysis

Twenty-nine of the thirty-three studies reported on all-cause mortality rate (n = 8738 participants) [10,21–26,59–65,68–77,79–83]. There was no significant difference in all-cause mortality rate between IVM and controls (RR 0.95, 95% CI 0.75–1.21, $I^2 = 0\%$; Fig. 2).

Seventeen of the thirty-three studies reported on MV requirement (n = 6049 participants) [10,24–26,59,60,64,65,68–72,75,76,81,82], and significant difference was observed between the two groups (RR 0.67, 95% CI 0.47–0.96, $I^2 = 0\%$; Fig. 3).

13 of the 33 studies reported on PCR negative conversion (n = 2023 participants) [25,60,62,66–70,72,73,75,77,79,81], but no significant difference was observed between the two groups (RR 1.00, 95% CI 0.94–1.07, $I^2 = 31\%$; Fig. 4).

19 of the 33 studies reported on AEs (n = 7411 participants) [10,23,26,59,60,64,68,70–76,79–83], and significant difference was observed between IVM and controls (RR 0.87, 95% CI 0.80–0.95, $I^2 = 19\%$; Fig. 5).

No significant difference was observed in LOS (MD 0.10, 95% CI -1.02 to 1.22, $I^2 = 54\%$; Supplementary Fig. 2), viral clearance (RR 0.95, 95% CI 0.83–1.10, $I^2 = 0\%$; Supplementary Fig. 3), admission to ICU (RR 0.93, 95% CI 0.66–1.30, $I^2 = 0\%$; Supplementary Fig. 4), symptoms resolved (RR 0.98, 95% CI 0.89–1.06, $I^2 = 64\%$; Supplementary Fig. 5), discharged from hospital (RR 1.08, 95% CI 1.00–1.15, $I^2 = 0\%$; Supplementary Fig. 6), or SAEs (RR 1.28, 95% CI 0.70–2.34, $I^2 = 0\%$; Supplementary Fig. 7) between the two groups.

3.3. Subgroup analyses

Subgroup analysis was performed by the controls. There was no significant difference in all-cause mortality rate between IVM and placebo (RR 1.11, 95% CI 0.83–1.48, $I^2 = 0\%$), between IVM and SOC with no placebo (RR 0.64, 95% CI 0.35–1.17, $I^2 = 0\%$), or between IVM and SOC with placebo (RR 0.82, 95% CI 0.44–1.51, $I^2 = 0\%$; Supplementary Fig. 8).

3.4. Sensitivity analysis and publication bias

Sensitivity analysis excluding small sample size studies (n < 60) showed that there was no significant difference in all-cause mortality rate (RR 0.95, 95% CI 0.75–1.21, $I^2 = 0\%$; Supplementary Fig. 9), which remained consistent with the overall analysis.

The funnel plot for all-cause mortality rate was symmetrical by visual inspection, indicating no publication bias in this study (Supplementary Fig. 10).

4. Discussion

Our meta-analysis included thirty-three RCTs (n = 10,489), which comprehensively reviewed the evidence on IVM treatment of patients with COVID-19 up to June 22, 2023 and showed that IVM did not have an effect in reducing the risk of mortality in patients with COVID-19. However, IVM had an effect on reducing the risk of AEs and MV requirement. Additionally, IVM did not increase the risk of PCR negative conversion, LOS, viral clearance, admission to ICU, symptoms resolved, discharged from hospital, hospitalization

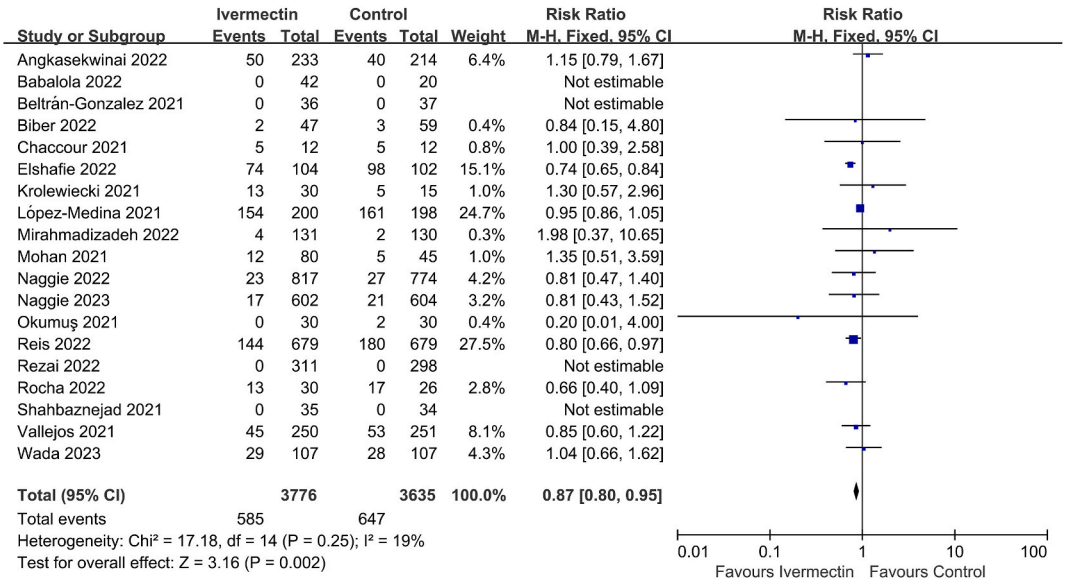

Fig. 5. Effect of ivermectin on adverse events in patients with COVID-19.

due to progression, or SAEs. Subgroup analysis based on different controls showed that IVM did not have an effect on reducing all-cause mortality rates in patients with COVID-19. In addition, subgroup analysis by severity of COVID-19 patients, IVM showed no effect on all-cause mortality rate between IVM and SOC, either. Which was consistent with the overall analysis when excluded small sample size studies ($n < 60$) or studies with follow-up < 21 days.

Despite not being recommended in the current guidelines by WHO or IDSA [33,84], IVM was one of the drugs and substances frequently used in self-medication in patients with COVID-19 [85–87]. Self-medication was related to the massive dissemination of misleading information, individual fear of contracting the virus, and limited access to healthcare services [85]. With the publication of overwhelming number of studies on COVID-19, it is an insurmountable challenge to keep the living reviews updated. IVM has been the subject of two living reviews. One living review was updated in August 2022, and pooled the evidence from forty-nine studies. Which suggested a reduction in mortality with IVM (RR 0.69, 95% CI 0.50–0.95), however, the effect was no longer apparent when included only the studies of low risk of bias (RR 1.00, 95% CI 0.80–1.24) [88]. The other suggested that IVM might reduce the mortality in patients with COVID-19 compared with control (RR 0.63, 95% CI 0.37–1.05), and highlighted the fact that the certainty of the evidence for IVM is low [89]. The two living reviews were not updated after the studies of Elgazzar et al., Pott-Junior et al., and Samaha et al. were retracted. Evidence shows that the use of hydroxychloroquine (HCQ) is harmful [90]. Therefore, future updates should not keep in the pooled analysis the studies that compared IVM with HCQ.

Different from our results, another review [91] included some studies in which IVM was compared with HCQ [19,57,92]; and another recent review [93] included the Pott-Junior et al. retracted trial [28]. We strongly believe that such studies should not be included in the best available body of evidence now. In additional, several studies have been published after these two reviews [21,23,26,63,70,80].

One strength of this review is that, in addition to the traditional search, the Living Overview of Evidence database (L.OVE, issued by Epistemonikus) was also used to conduct a comprehensive search. L. OVE is a digital tool that can compile studies from several databases (including preprint databases), and is updated through computational algorithms [94]. Which may be more convinient to update the search regularly and more efficient than the traditional search [95]. Misleading information may be obtained when inappropriate methods are used. Therefore, another strength of this review is the application of strict methodological criteria. Our review analyzed not only studies comparing IVM with placebo, but also those comparing IVM with SOC, in a stratified analysis. Additionally, stratified analysis based on the severity of COVID-19 was performed.

This study has several limitations. First, all-cause mortality rate, MV requirement, PCR negative conversion, and AEs are primary outcomes, and the certainty of the evidence for these outcomes were ranked as moderate owing to some concerns about imprecision and risk of bias. Methodological limitations were mainly associated with data integrity, design of included studies, and potential conflicts of interests. Additional concerns were that some studies did not pre-register prior to recruiting participants, while others had revised the protocol. However, as LOS was negative, these potential sources of bias may not have had a significant impact on these outcomes. Another limitation lies in the low incidence of event. Among the 29 studies examining for all-cause mortality, 15 did not have any events. Therefore, the overall all-cause mortality rate should be very low in this context. The majority of the included studies enrolled participants with mild-to-moderate COVID-19, but the severity of disease varied among them. To overcome this limitation, a subgroup analysis was conducted and no significant effect modification was found in each subgroup. Which also applies for MV requirement. Last, our meta-analysis included studies with small sample size, which may overstate the benefits of this intervention. To address this limitation, we performed a sensitivity analysis by excluding studies with small sample size, which found significant effect

modification of MV requirement.

The urgent need for COVID-19 treatment options has spurred a surge in RCTs, which led to the perform and publication of studies with uneven quality and notable methodological shortcomings. This provided fertile ground for even poorly evidence to be exaggerated not only on social media but also in the scientific literature [27]. The consequence is very serious because the outcomes from studies with high risk of bias would spread rapidly in clinical practice, and these drugs would also be incorporated into public policies or as SOC among different countries and regions hastily. To make matters worse, some researchers and institutions were reluctant to change the protocols after the evidences against the use of certain drugs [15]. Consequently, studies have enrolled uneven and clinically inappropriate options due to defining their comparators as standard of care. For example, a research protocol was registered in Brazil [96] following evidence that HCQ can increase the risk of all-cause mortality. In May 2020, the WHO recommended against the use of antibiotics as standard of care in COVID-19 patients without evidence of bacterial pneumonia; however, two later studies kept antibiotics in their definition of standard of care [22,81].

Furthermore, we sought to minimize potential biases during the review process based on the methods recommended by the Cochrane Collaboration [96] and prescribed in our PROSPERO protocol.

In a recent publication, the authors reported that in addition to the retracted trials, several others claiming benefits for IVM may be equally of concern. Which emphasized that trial registry updates could not explain the incompatibility between published participant demographics and timelines that are inconsistent with the authenticity of the data collection [27]. Therefore, it is critical for reviewers to keep updated with potential new retractions in time before following strict methodological standards. A number of supporters, many of whom are anti-vaccination activists, have continued to vigorously promote the use of IVM, claiming that real evidence has been ignored. Some websites have released systematic reviews on the effectiveness of IVM for COVID-19 (covid19criticalcare.com) and (https://ivmmeta.com). Most of which are not peer-reviewed, do not present the eligible criteria used in the selection process, and do not display statistical criteria for assessing the effectiveness and heterogeneity among included studies. These websites, according to Roman et al., provide misinformation to health professionals, patients, and the general population who are unable to critically analyze scientific studies. Our thorough and transparent review may contribute to disseminate authentic evidence. Although the incidences of AEs and PCR negative conversion were lower in IVM group, the incidence of SAEs was comparable between the two groups. As associated with a certain clinical benefit, these should be taken into account in the management of patients with COVID-19.

5. Conclusion

In summary, ivermectin could reduce the risk of mechanical ventilation requirement and adverse events in patients with COVID-19, without increasing other risks. Despite no conclusive evidence or guidelines recommending ivermectin as a therapeutic drug for COVID-19, clinicians could use it with caution in the absence of better alternatives, and self-medication of ivermectin is not recommended for patients with COVID-19.

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Declaration of interest's statement

The authors declare no competing interests.

Data availability statement

Data included in article/supp. Material/referenced in article. Data will be made available on request.

CRediT authorship contribution statement

Zhilong Song: Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Senyuan Shi:** Validation, Software, Resources, Project administration, Methodology, Investigation. **Yongli Zhang:** Writing – review & editing, Visualization, Supervision, Formal analysis, Data curation, Conceptualization.

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.e27647.

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