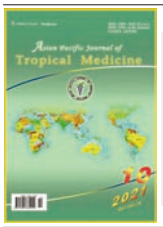

Meta-Analysis

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Efficacy and safety of ivermectin for COVID-19: A systematic review and meta-analysis

Alok Singh✉, Pranav G Sheth, Suryaprakash Dhaneria, Dhyuti Gupta

Department of Pharmacology, All India Institute of Medical Sciences, Raipur 492099 Chhattisgarh, India

ABSTRACT

Objective: To critically evaluate the trials that have assessed the efficacy and safety of ivermectin COVID-19 and to validate the rationality of using this drug in the management of COVID-19 either as a prophylactic or therapeutic agent.

Methods: The authors conducted a systematic search through various databases, *i.e.*, Cochrane library, PubMed, clincialtrials.gov, and preprint servers, for publications from 2020 to May 2021. The keywords used for the search were: "COVID-19 and ivermectin" (with filter set for "trials"). All the trials assessing efficacy in prophylaxis and treatment of COVID-19 were included for analysis. The primary outcome was the proportion of patients showing disease progression. Secondary outcomes were mean duration of hospitalization and resolution of symptoms, the proportion of patients testing positive on day 5-7, the mortality rate in severe cases, incidence of serious adverse events, and contacts of COVID-19 positive patients who turned RT-PCR positive after prophylaxis treatment.

Results: A total of 17 clinical trials were included for the evaluation. Ivermectin proved to be a beneficial add-on therapy, as it reduced the risk of disease progression (*OR* 0.47, 95% *CI* 0.30-0.74, *P*=0.001), led to early resolution of symptoms (MD -1.16, 95% *CI* -1.52--0.81, *P*<0.001), and had less duration of hospitalization (MD -2.21, 95% *CI* -3.23--1.19, *P*<0.001). In addition, ivermectin was better in providing effective prophylaxis (*OR* 0.13, 95% *CI* 0.05-0.30, *P*<0.001). The incidence of serious adverse events was low.

Conclusions: As an adjunct to standard care, ivermectin has shown its efficacy and safety in treating and prophylaxis in COVID-19 disease. These results should be interpreted cautiously as these trials had significant shortcomings.

KEYWORDS: Ivermectin; SARS-CoV-2; COVID-19; Drug repurposing; WHO

1. Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, was declared a global pandemic by World Health Organization (WHO) in March 2020[1,2]. The disease was first detected in December 2019 and has led to more than 4.6 million deaths globally[3,4]. The incubation period of this disease can vary from 2-14 days and result in either symptomatic or asymptomatic infection. The symptoms, usually of mild-to-moderate intensity, can range from fever, cough, shortness of breath, muscle ache, loss of taste and smell and fatigue to gastrointestinal manifestations. There is associated development of hypercoagulable state and lung damage in case of severe infection, which can progress to interstitial pneumonia, acute respiratory distress syndrome, and subsequently to multiorgan failure[3-6]. To date, no effective therapeutic agent could be discovered and proved to be curative. Moreover, in such situations identifying and developing a new therapeutic molecule is both time-consuming and economically challenging, as well as providing vaccination cover to all will take

Significance

Ivermectin is claimed to be beneficial in treatment and prophylaxis of COVID-19 illness. The authors via the systematic search and meta-analysis assessed the benefits of ivermectin in COVID-19. By the present study, authors have tried to answer whether the ivermectin should be recommended for the management of COVID-19 illness. The study will be helpful in promoting rational use of ivermectin in COVID-19.

✉To whom correspondence may be addressed. E-mail: draloksingh@aiimsraipur.edu

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years. In such scenario, identifying the already marketed drugs which could be repurposed in managing this syndrome may prove to be more fruitful and feasible, especially in developing countries. To list a few repurposed drugs which are already being evaluated for this said condition are antivirals (lopinavir/ritonavir, remdesivir, favipiravir), antimicrobials (doxycycline, azithromycin, ivermectin), antimalarial (hydroxychloroquine), anti-IL6 receptor antibody (tocilizumab), glucocorticoids, antithrombotic and so on[7,8].

Recently, the spotlight has shifted onto a widely used anti-helminthic drug, ivermectin, which has demonstrated antiviral activity against SARS-CoV-2 *in-vitro*[9]. The mechanism behind this activity is the ability of ivermectin to inhibit importin $\alpha/\beta1$ (a type of karyopherin)-mediated transport of viral proteins back and forth host cell nucleus, thus occupying the host cell machinery for replication and generation of viral progenies[8]. The usual dose of this drug is 0.2-0.4 mg/kg, with a half-life of about 18 hours, and undergoes hepatic metabolism. Its bioavailability gets increased if consumed after a high-fat meal. Furthermore, the commonly encountered adverse effects of its use are dizziness, pruritus, diarrhea, nausea, and other gastrointestinal effects[10]. Considering the different mechanisms of antiviral activity, wider safety margin, and cost-effective treatment offered by ivermectin, it does become a potential therapeutic agent that can be explored in the management of COVID-19, either prophylactically or curatively[8,11]. The dosing schedule for the same has been proposed as 200 mcg/kg once a day for 3-5 days[12,13]. Nevertheless, for ivermectin to demonstrate the similar anti- COVID-19 activity as observed *in-vitro*, the dose has to be escalated up to 100 times of the approved dose for human use. Also, its concentration in lung tissue is remarkably less than the concentration at which 50% viral inhibition occurred *in-vitro*[14,15].

International organizations like World Health Organization (WHO) have recommended restricted use of this anti-helminthic to clinical trials only, yet there is rampant use of ivermectin in many countries[16,17]. Since the data regarding using this drug, either as prophylactic or curative in COVID-19, is insufficient, there is a need to conduct well-designed and competent clinical trials to grasp ivermectin's exact role and effectiveness in subduing this pandemic[18]. Taking into account these disparities, the competency of ongoing trials for ivermectin as well as the urgent need for evidence-based guidelines for tackling this global pandemic, the authors planned to conduct a systematic review to substantiate the rationality behind the use of ivermectin either as a prophylactic or curative agent in the management of COVID-19 disease.

2. Materials and methods

The current meta-analysis was performed as per the *Guidelines of preferred reporting items for systematic reviews and meta-analyses statement*, for which ethical permission is not essential[19].

2.1. Literature search and data extraction

Two of the authors performed the systematic search (A.S. and P.S.) among the databases PubMed, Cochrane library, Clinical Trial Registry (https://clinicaltrials.gov/), and preprint servers like medRxiv.org and research square for a timeline from 2020 to May 2021 using the keywords: "COVID-19 and ivermectin;" with the filter "trials." Previously conducted meta-analyses were also searched for discussion.

2.2. PICOS criteria

Patients: Adults COVID-19 illness (mild to severe).

Intervention/Comparator: Ivermectin (12-48 mg/d) was used as an add-on therapy to standard care. As the pandemic is going on, we included all the studies which assessed the efficacy of ivermectin in prophylaxis and treatment of COVID-19 disease administered as a tablet, elixir, or topical formulation. The studies comparing ivermectin with other unproven drugs in the management of COVID-19 illness were not included.

Primary outcome:

•The proportion of patients who showed progression of the disease or clinical worsening.

Secondary outcomes:

•Mean duration of hospital stay.

•Mean duration of resolution of symptoms or clinical recovery.

•The proportion of patients who were tested positive on days 5-7.

•The mortality rate in severe/critical COVID-19 patients.

•The proportion of contacts who were tested positive with RT-PCR (prophylaxis *i.e.*, prevention of COVID-19 infection in contacts of COVID-19 positive patients.).

•Incidence of serious adverse events.

Study design: All the clinical trials assessing the efficacy of ivermectin in prophylaxis and treatment of COVID-19 were included. The demographic data and essential characteristics of clinical trials were also documented. The data extraction was performed by three of the authors and duly verified with one another.

2.3. Risk of bias assessment

The individual trial was checked for its quality by performing the risk of bias assessment as per *Preferred reporting items for systematic reviews and meta-analyses guidelines* and shown in the forest plot[20]. The trial quality was also assessed using Jadad's scale. In Jadad's scale, we analyze randomization (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-1 points). Five is the maximum score for a trial, and the trials with score 3 are considered high quality[21].

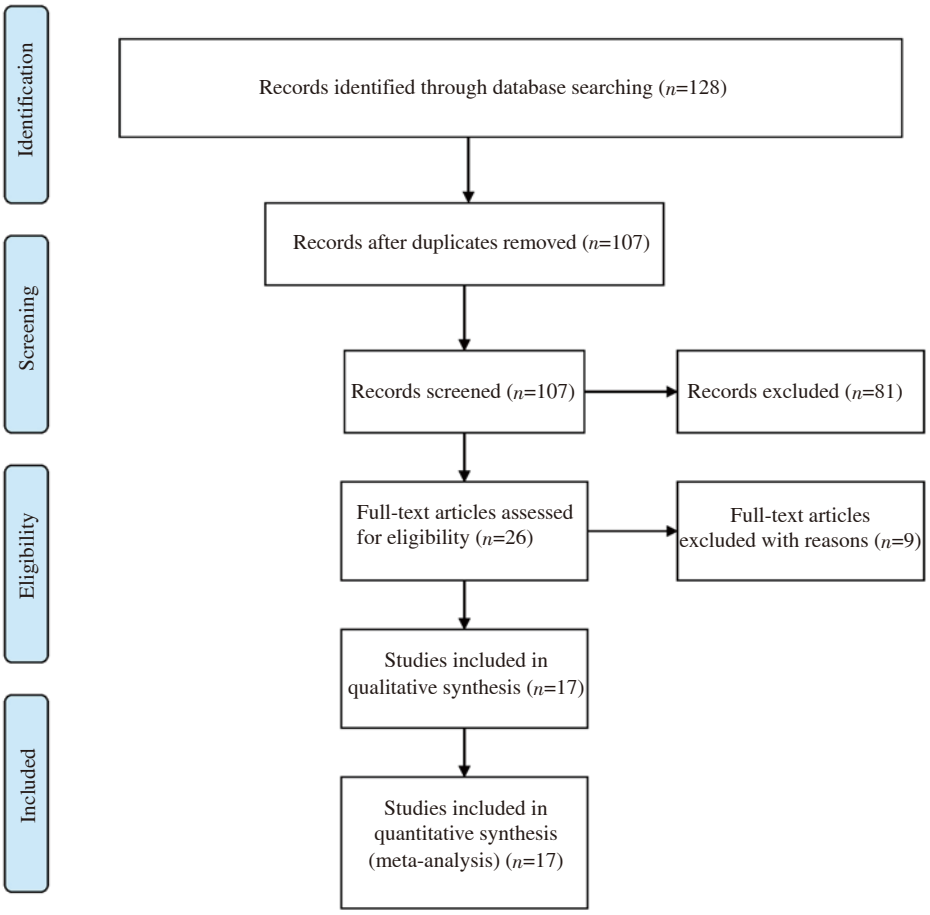


Figure 1. Flow diagram of study selection process.

2.4. Statistical analysis

We assessed the odds ratio (*OR*) and mean difference (MD) with a confidence interval (*CIs*) of 95% for dichotomous and continuous variables, respectively. In case of any missing data (standard deviation), the highest values were imputed from other studies for the same parameter[22]. In few studies, the in-place of mean and standard deviation (SD), median, and range were mentioned; hence mean, and SD was derived from given data[23]. I^2 statistic (I^2>50% indicated heterogeneity) was applied to assess heterogeneity among the included studies[24]. This meta-analysis was performed using a random-effect model with Review Manager (Rev Man) v5.4 for windows. Furthermore, we obtained a funnel plot and performed egger's test to assess publication bias[25].

3. Results

3.1. Literature search and study characteristics

Initially, the authors found 128 records, and after the removal of duplicates, 107 were left. On further scrutinizing, 28 studies were sorted for analysis[26-53]. Out of 28 studies, two studies were excluded as they were retrospective in nature and eventually 26 prospective studies were left (Figure 1)[26,27]. On further screening, four studies were excluded as the endpoints were not similar to the desired endpoints[29,46,47,53]. One study was excluded due to incomplete information available to authors[41]. Another study comparing the outcome of different treatment protocols was excluded as it has different endpoints[35]. Two more studies were not included due to the faulty trial design comparing ivermectin (investigation agent) effects with other therapy of unproven benefits[33,40]. Lastly, in the study, a comparison of combinations of different drugs was assessed against ivermectin; hence the study was excluded from further discussion[39]. The relevant characteristics of the 26 prospective studies have been mentioned in Table 1[28-53]. Six out of 17 included studies scored <3 in Jadad's score[30-32,34,42,51]. Only five studies were free of significant bias[37,38,45,48,50]. Among the included studies, 2 928 patients (24-600) were enrolled, and 42.4% were female. The diagnosis of COVID-19 among all the studies was established based on the RT-PCR test. In a few studies, the standard deviation (SD) for continuous data was missing; hence these values were imputed from other studies with maximum values being considered[32,34]. Similarly, few studies did not have mean and SD in results, so they were calculated from median and range[37,38,49].

Table 1. Salient features of included clinical trials[28–53].

Study	*N*	Study design	Primary endpoint (s)	Dose	Age (years)	%	Jadad score
Chahla *et al*. NCT04701710	234	Randomized controlled-trial	Reduction the infections rate for COVID-19 disease in healthcare agents (RT-PCR)	IVM 12 mg/d every 7 days, and iota-carrageenan 6 sprays per day for 4 weeks	EG: 39.6±9.4 CG: 38.4±7.4	134/234	3
Shoumann *et al*. 2021 NCT04422561	304	Randomized controlled-trial	Reduction in development of symptoms suggestive of COVID-19	IVM 15-24 mg/d (depending on body weight) on day 1 and 3	EG: 39.75±14.93 CG: 37.69±16.95	148/304	1
Hector *et al*. 2020 NCT 04425850	229	Cohort study	Incidence of detection of COVID-19 by PCR Incidence of appearance of symptoms related to COVID-19 infection	A combination of carrageenan and ivermectin (into nostrils and oral cavity)	N/A	123/229	1
Elgazzar *et al*. NCT04668469	600	Randomized controlled-trial	Clinical, laboratory improvement and/or 2 consecutive negative PCR tests taken at least48 hours apart, hospital stay days COVID-19 infection in others	IVM 400 μg/kg for 4 days for treatment; IVM 400 μg/kg weekly	Group 1: 56.7±18.4 Group 2: 53.8±21.3 Group 3: 58.2±20.9 Group 4: 59.6±18.2 Group 5: 57.6±18.4 Group 6: 56.8±18.2	172/600	1
Ahmed *et al*. 2021	72	Randomized double-blind placebo-controlled trial	Time required for virological clearance	IVM 12 mg/d for 5 days; Doxycycline 200 mg for 5 days	N/A	39/72	1
Chowdhury *et al*. NCT04434144	116	Randomized controlled-trial	Recover time to negative PCR and resolution of symptoms	IVM 200 μg/kg single dose+doxycycline 100 mg *bid* for 10 days; HCQ 400 mg 1st day then 200 mg *bid* for 9 days+azithromycin 500 mg daily for 5 days	Group A: 35.72±15.1 Group B: 31.91±12.72	26/116	3
Gorial *et al*. NCT04343092	87	Cohort study	Percentage of cured patients time to stay in the hospital	Single dose of IVM 200 μgm/kg/d in addition to HCQ and azithromycin	Group A: 44.87±10.64 Group B: 45.23±18.47	24/87	1
Hector *et al*. NCT04425863	167	Cohort study	Percentage of patients progressing from mild to moderate or severe stages of disease to mortality rate by day 30	IVM 24-48 mg solution dexamethasone 4 mg injection daily aspirin 250 mg tablet once daily for at least 30 days enoxaparin 1 mg/kg daily	N/A	81/167	1
Okumus *et al*. 2021 NCT04646109	60	Randomized single-blind placebo-controlled trial	Clinical responses and drug side effects obtained in patients on the 5th day	IVM 200 μgm/kg/d for 5 days in addition to reference treatment	EG: 58.17±11.52 CG: 66.23±13.31	20/60	3
Mahmud *et al*. 2021 (NCT04523831)	400	Randomizeddouble- blind placebo- controlled trial	Number of days required for clinical recovery anddisease progression	IVM 12 mg single dose+doxycycline 100 mg BD for 5 days	EG: 41±14 CG: 38±12	165/400	5
Medina *et al*. 2021 NCT04405843	400	Randomized double blind placebo controlled trial	Median time for resolution of symptoms, the proportion of patients with clinical deterioration	IVM 300 μg/kg of body weight per day for 5 days placebo	EG: 37 (29-47.7) CG: 37 (28.7-49.2)	238/400	5
Elalfy *et al*. 2021 NCT04392427	113	Non randomized, controlled trial	Rate and time of viral clearance	<60 kg-18 mg OD 60–90 kg-18 mg OD 90–120 kg-24 mg OD >120 kg-30 mg OD	EG: 37.5±10.9 CG: 37.9±11.9	61/113	1
Galan *et al*. 2021	168	Randomized double-blind active comparator	Need of supplemental oxygen, invasive ventilation, admission in ICU and death	⩾55 kg 14 mg OD <55 kg 10 mg OD	CQ: 51.9±14.0 HCQ: 54.8 ±15.5 IVM: 51.9±14.0	68/163	5
Raad *et al*. ChiCTR2000033627	100	Single-blind randomized Controlled trial	Risk of hospitalization,viral load	IVM 200 μg/kg single dose	N/A	N/A	N/A
Hashim A *et al*. 2021 NCT04591600	140	Randomized controlled study	Time to recovery, the progression of the disease, and the mortality rate	IVM 200 μg/kg PO per day for 3 days along with doxycycline bd for 5-10 days and standard care	EG: 50.1±9.3 CG: 47.2±7.8	68/140	2
Bukhari *et al*. 2021 NCT04392713	100	Randomized non-blinded trial	Days to achieve PCR negative, development of any adverse side effects	IVM 12 mg single dose along with standard care	EG: 42.2±12.0 CG: 39.0±12.6	13/86	3
NCT04407507	66	Randomized non-blinded placebo-controlled trial	Controlled disease defined as no disease progression to severe, SARS-CoV-2 viral load, at 5 and 14 days	IVM 12 mg/d for 3 days	EG: 40.24 CG: 36.82	48/66	N/A
Chaccour *et al*. 2021 NCT04390022	24	Randomized double-blind placebo-controlled trial	The proportion of patients with detectable SARS-CoV-2 RNA by PCR, viral load at days 4, 7, 14 and 21 post-treatment	IVM 400 mcg/kg, single dose placebo	EG: 26 (19-36) CG: 26 (21-44)	12/24	5
Babalola *et al*. 2021 ISRCTN40302986	62	Randomized, controlled, double- blind	Days to COVID negative	IVM: 6 and 12 mg weekly for two weeks	EG: 48.3 CG: 44.8	19/62	1
Chachar *et al*. 2020	50	Randomized controlled trial	Asymptomatic and symptomatic patients at day 7	IVM 3 doses of 12 mg 12 hourly apart	EG: 40.6±17.0 CG: 43.08±14.80	19/50	2
Mohan *et al*. 2021	125	Randomized double-blind placebo-controlled trial	Proportion of patients RT-PCR negative at day 5, clinical worsening, and mean days for symptoms resolution	IVM as elixir formulation 12, 24 mg. Placebo	EG: 34.30±10.45 CG: 35.30±10.52	14/125	5
Niaee *et al*. 2021	180	Randomized double-blind placebo-controlled trial	Duration of hospital stay, low oxygen saturation, fever and tachypnoea	IVM: single dose ivermectin (400 μg/kg). Standard included HCQ: 200 mg *bid*	EG: 54 (47-60) CG: 55 (45-70)	90/180	3
Ravikirti *et al*. 2021	112	Randomized double-blind placebo-controlled trial	Proportion of patients with negative RTPCR at day 6, progression of disease, ICU admission, and invasive ventilation	IVM 12 mg/d on day 1 and 2. Placebo	EG: 50.7±12.7 CG: 54.2±16.3	31/112	5
Podder *et al*. 2020	62	Open-label, randomized controlled study	Time required for resolution of symptoms	IVM 200 micrograms/kg single dose	EG: 38.41±11.02 CG: 39.97±13.24	18/44	1
Shahbaznejad *et al*. 2021	69	Double-blind, randomized, controlled trial	Time of hospital stay, and overall clinical improvement	IVM: single dose 0.2 mg/kg	EG: 47.63±20.20 CG: 45.18±23.11	33/69	3
Pott-Junior *et al*. 2021	32	Randomized open-label trial	Viral load within 7 days, adverse effects	IVM 100, 200, 400 micrograms/kg	EG: 49.0±13.5 CG: 54.2±9.6	17/31	3

IVM: Ivermectin; HCQ: Hydroxychloroquine; CQ: Chloroquine; EG: Experimental group; CG: Control group; N/A: Not available.

3.2. Primary outcome

Based on the funnel plot, we did not observe any publication bias (Figure 2). Same was substantiated by Egger's calculation [-0.247 933 (95% *CI* -1.925 825-1.429 959), *P*=0.670 2]. The heterogeneity was not observed [I^2=0% (95% *CI* 0%-64.1%), *P*=0.99] among these trials (Figure 3). In the ivermectin group, proportion of patients who showed progression of the disease or clinical worsening was significantly lower than standard therapy (*OR* 0.47; 95% *CI* 0.30-0.74; *P*=0.001) (Figure 3).

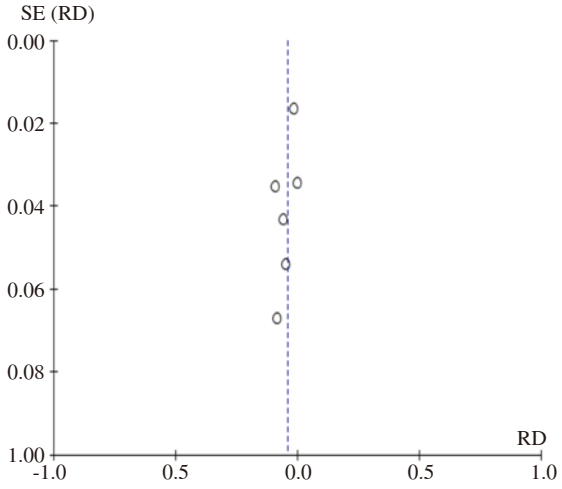


Figure 2. Funnel plot for primary outcome.

3.3. Secondary outcomes

There was significant difference was observed in mean duration of hospital stay and mean time to resolution of symptoms [MD=-2.21, (95% *CI* -3.23--1.19), *P*<0.000 01] (Figure 4); MD=-1.16, 95% *CI* -1.52--0.81, *P*<0.000 01 (Figure 5)]. There was no significant difference was noted in proportion of patients who were tested positive on day 5-7 and similar trend was noted in mortality rate in severe/critical COVID-19 illness (*OR* 0.37, 95% *CI* 0.10-1.29, *P*=0.12) (Figure 6); (*OR* 0.45, 95% *CI* 0.17-1.18, *P*=0.10) (Figure 7). The ivermectin group was superior in the prophylaxis of COVID-19 infection in contacts of COVID-19 positive patients than the standard group, which used only personal protective equipment, and the difference was statistically significant (*OR* 0.13, 95% *CI* 0.05-0.30, *P*<0.000 01) (Figure 8). The detailed analysis of evidence is present in Table 2. Funnel plots for individual outcome are available as supplementary material.

The meta-analysis of the incidence of serious adverse events was not performed, however, only five studies mentioned the serious adverse events[35,37,38,40,44]. The study by Hector *et al.* has reported a serious adverse event (gastric ulcer) that was attributable to dexamethasone[35]. In a study, two patients discontinued the ivermectin due to erosive esophagitis[37]. In another study, four serious adverse events were observed, but none of them was attributable to ivermectin[38]. The study conducted has reported anemia (Hb<8 g/dL) and leucopenia (<1 500/mm^3)[40]. A serious adverse event (encephalitis) was reported in one of the trials[44].

4. Discussion

The present meta-analysis aimed to assess the role of ivermectin as add-on therapy in the management of treatment and prophylaxis of COVID-19 illness. The study included the clinical trials published or available up to 31st May 2021. In our results, most of the patients were male, following the usual epidemiological trend of COVID-19 illness[54]. The total number of patients included in the meta-analysis

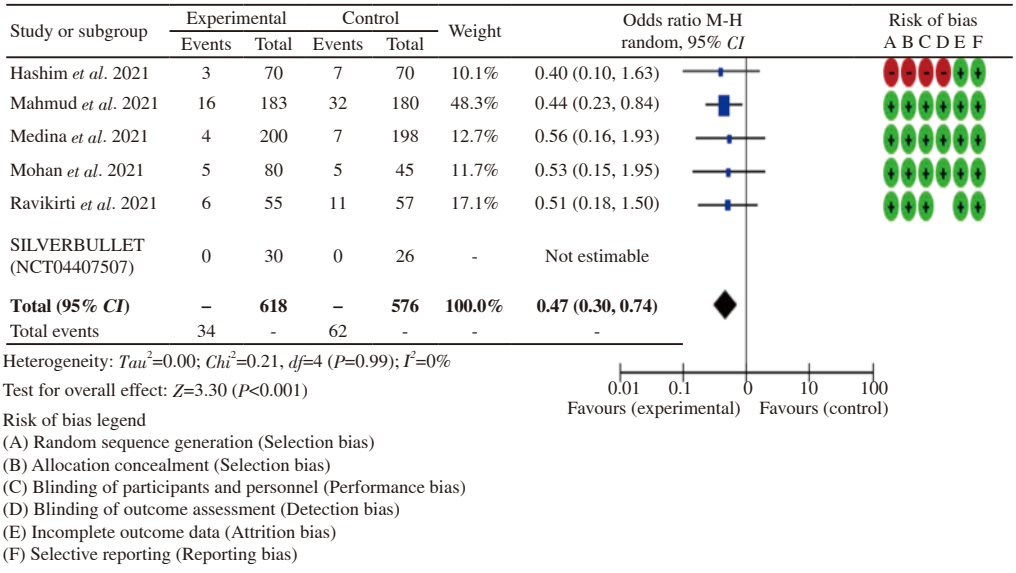
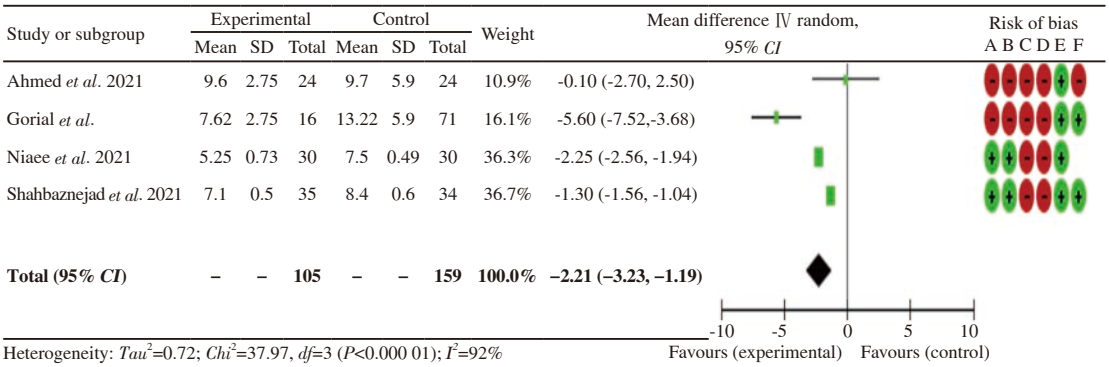


Figure 3. Forest plot for proportion of patients who showed progression of the disease or clinical worsening

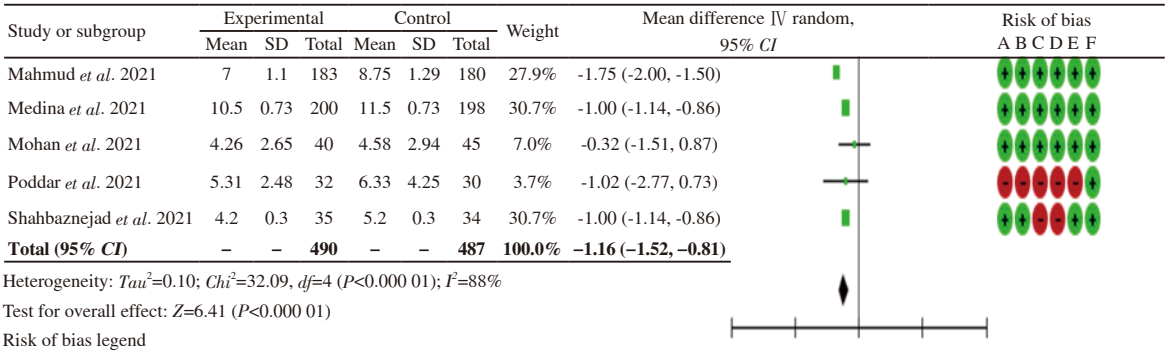


Heterogeneity: Tau^2=0.72; Chi^2=37.97, df=3 (P<0.000 01); I^2=92%

Test for overall effect: Z=4.23 (P<0.000 1)

Risk of bias legend
(A) Random sequence generation (Selection bias)
(B) Allocation concealment (Selection bias)
(C) Blinding of participants and personnel (Performance bias)
(D) Blinding of outcome assessment (Detection bias)
(E) Incomplete outcome data (Attrition bias)
(F) Selective reporting (Reporting bias)

Figure 4. Forest plot for mean duration of hospital stay.

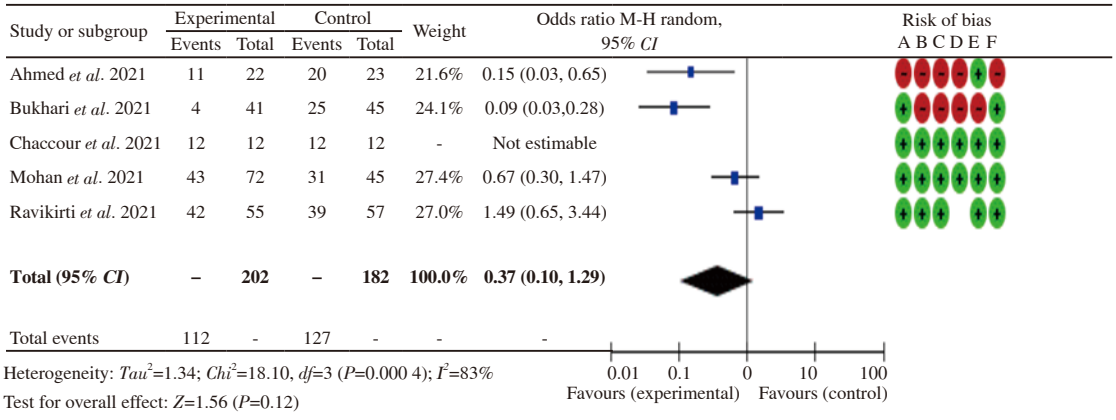


Heterogeneity: Tau^2=0.10; Chi^2=32.09, df=4 (P<0.000 01); I^2=88%

Test for overall effect: Z=6.41 (P<0.000 01)

Risk of bias legend
(A) Random sequence generation (Selection bias)
(B) Allocation concealment (Selection bias)
(C) Blinding of participants and personnel (Performance bias)
(D) Blinding of outcome assessment (Detection bias)
(E) Incomplete outcome data (Attrition bias)
(F) Selective reporting (Reporting bias)

Figure 5. Forest plot for mean duration of resolution of symptoms or clinical recovery.



Heterogeneity: Tau^2=1.34; Chi^2=18.10, df=3 (P=0.000 4); I^2=83%

Test for overall effect: Z=1.56 (P=0.12)

Risk of bias legend
(A) Random sequence generation (Selection bias)
(B) Allocation concealment (Selection bias)
(C) Blinding of participants and personnel (Performance bias)
(D) Blinding of outcome assessment (Detection bias)
(E) Incomplete outcome data (Attrition bias)
(F) Selective reporting (Reporting bias)

Figure 6. Forest plot for the proportion of patients who were tested positive on day 5-7.

Table 2. Certainty assessment and summary of findings.

Primary endpoint(s)	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	No. of patients		Effect	
							Ivermectin prescribed as an add-on	Standard treatment	*OR* (95% *CI*)	Absolute (95% *CI*)
Incidence of infection checked by RT-PCR	3	Randomised trials	Very serious[a]	Not serious[b]	Very serious[c]	Very serious[d]	6/348 (1.7%)	46/315 (14.6%)	0.13 (0.05-0.30)	124 fewer per 1 000 (from 138 fewer to 97 fewer)
Mean duration of hospital stay	4	Randomised trials	Very serious[a]	Very serious[e]	Serious[f]	Very serious[d]	105	159	-	MD 2.21 lower (3.23 lower to 1.19 lower)
Proportion of patients showing progression of disease	6	Randomised trials	Not serious	Not serious[b]	Very serious[g]	Very serious[d]	34/618 (5.5%)	62/576 (10.8%)	0.47 (0.30-0.74)	54 fewer per 1 000 (from 73 fewer to 26 fewer)
Mean duration for resolution of symptoms	5	Randomised trials	Not serious	Very serious[h]	Very serious[g]	Very serious[d]	490	487	-	MD 1.16 lower (1.52 lower to 0.81 lower)
Mortality rate in severe COVID-19	2	Randomised trials	Very serious[a]	Not serious[i]	Serious[g]	Very serious[d]	8/52 (15.4%)	15/52 (28.8%)	0.45 (0.17-1.18)	134 fewer per 1 000 (from 224 fewer to 35 more)
Proportion of patients RT-PCR positive on day 5-7	5	Randomised trials	Serious[j]	Very serious[k]	Very serious[g]	Very serious[d]	112/202 (55.4%)	127/182 (69.8%)	0.37 (0.10-1.29)	237 fewer per 1 000 (from 510 fewer to 51 more)

[a]problems with randomization and blinding; [b]I^2=0%; [c]differences in interventions and time frame; [d]sample size was not estimated; [e]I^2=92%; [f]difference in doses administered; [g]different dose for variable duration, doxycline as confounder; [h]I^2=88%; [i]I^2=0%; [j]problem in blinding and randomization in few studies; [k]I^2=83%. *CI*: Confidence interval; *OR*: Odds ratio; MD: Mean difference.

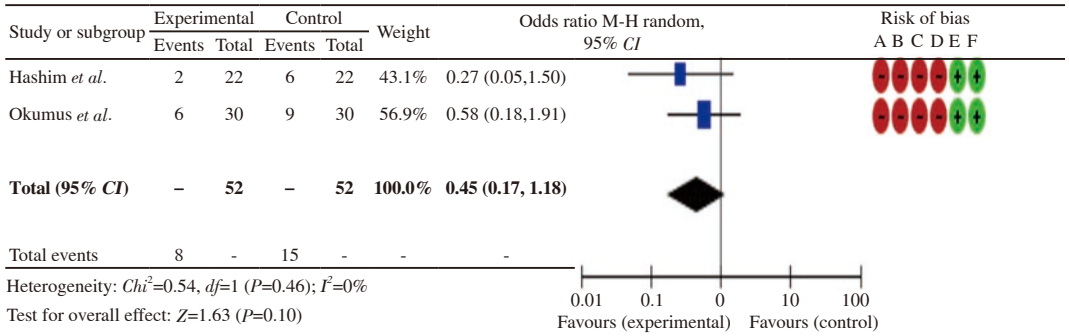
(*n*=2 928) is less than the gravity of illness worldwide, as more than 170 million people have been infected[4].

In many outcomes that we have selected for analysis, ivermectin as an add-on to standard care was effective. The studies included in assessing the proportion of patients showing the progression of the disease, mean days for resolution of symptoms, and duration of hospitalization have significant shortcomings that are worth mentioning[32,34,37,38,42,48–50,52]. The major limitation of all the studies is the lack of sample size estimation before the start of the study, and all had a small sample size. Though the disease progression was the endpoint in the studies, the method to judge the progression was not the same. Two of the studies included the WHO ordinal scale to assess progression, while others relied on the symptoms characteristics of different stages of the disease. Results are further complicated by inconsistent dosing schedules and variable routes of administration. It ranged from a single dose to 2-5 days in variable doses, *i.e.*, 200-300 μg/kg or 12-24 mg/d. The formulation was the same except one where it was administered as an elixir[48]. Furthermore, the use of doxycycline along with ivermectin makes the comparison more complex[37,42]. These factors are the potential sources of heterogeneity. Though the studies included for this endpoint are homogenous, a single study has disproportionate weight and contributes to 48.3% weight alone[37]. All studies included for this comparison are of good quality except one which seems to be at high risk for multiple biases, *i.e.*, selection, allocation, and detection bias[42].

Ivermectin as an add-on has also shown a significant prophylactic role in COVID-19 infection; however, it also requires careful evaluation of results. All the three studies included are at high risk of bias[28,30,31]. The issue of small sample size and its calculation remains the same. Though homogenous, one study has got disproportionate weight which may alter the results[28]. The variability of dose, duration, and route is also different, which is further complicated by simultaneous administration of carrageenan[28,30]. Hence, these significant results must be scrutinized before formulating the policy and recommendations.

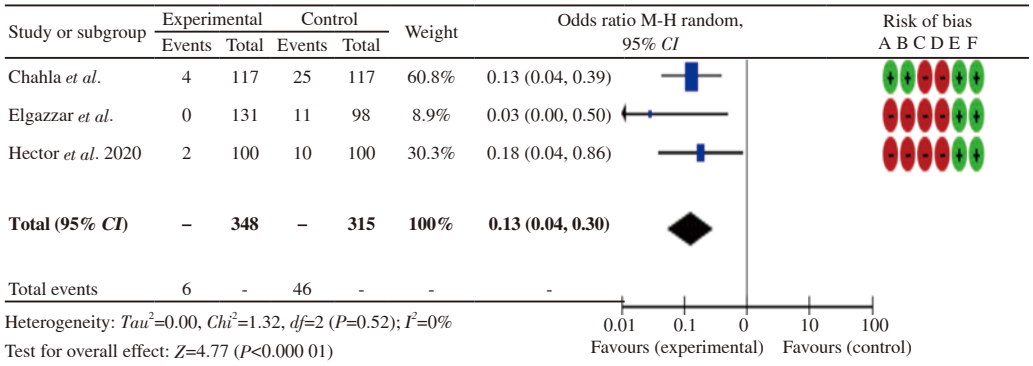
Ivermectin failed to show any significant effect in other outcomes, *i.e.*, RTPCR positivity rate after 5-7 days, and mortality rate. In a previous meta-analysis, the mortality benefit was observed by authors, but we did not observe any significant benefit as we included studies that assessed mortality in severe COVID-19 illness[55]. Since most patients with mild to moderate illness recover with appropriate medical support, there is no point in assessing mortality in mild to moderate disease.

Ivermectin is known to be remarkably safe[8]. In our review, we also noted very few serious adverse events attributable to the drug substantiating its record of safety. The more significant safety



Risk of bias legend
(A) Random sequence generation (Selection bias)
(B) Allocation concealment (Selection bias)
(C) Blinding of participants and personnel (Performance bias)
(D) Blinding of outcome assessment (Detection bias)
(E) Incomplete outcome data (Attrition bias)
(F) Selective reporting (Reporting bias)

Figure 7. Forest plot for the mortality rate in severe/critical COVID-19 patients.



Risk of bias legend
(A) Random sequence generation (Selection bias)
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(E) Incomplete outcome data (Attrition bias)
(F) Selective reporting (Reporting bias)

Figure 8. Forest plot for the proportion of contacts who were tested positive with RT-PCR (prophylaxis).

margin adds to the acceptability of drugs in the general public. Wider safety margin must not be the excuse for rampant and irrational use of ivermectin in COVID-19, especially in under-developed and developing world. The ivermectin is not recommended in the age group <15 years, and it should not be used in pregnant females and preferably avoided in nursing mothers[10].

Two retrospective case-control studies were also screened during evaluation, though the studies were well-designed and the outcome was favorable for ivermectin[26,27]. Since the case-control studies stand very low in the hierarchy of evidence, their data cannot be considered in formulating policy[56]. The fact which goes in favor of ivermectin as a prophylactic agent is the association of less COVID-19 incidence in few parts of the world (Africa), where it is given routinely as mass administration[57].

Another fact that is worth discussing is the concentration in which the ivermectin inhibits viral replication. It was estimated that IC_{50} of ivermectin is about 35 times higher than the C_{max} of the drug when administered in approved doses, and it is doubtful that desired concentration can be achieved practically despite having a wider therapeutic index (10 times up to 2 000 μg/kg)[58]. This is an essential factor that needs consideration in the interpretation of significant findings.

Our study supports the WHO mandate, *i.e.*, the use of ivermectin in COVID-19 is not recommended except in clinical trial settings[16]. The USFDA and EMA have advised not to use the ivermectin to prevent or treat COVID-19 disease[59,60]. In India, ivermectin has been used widely for COVID-19; however, it is recommended under low certainty of evidence[61,62]. In different parts of the world, the irrational use of ivermectin and other unproven therapies is widespread during the pandemic[61,63–65]. Self-medication has emerged as a significant problem in the pandemic, especially in countries with poor regulation over drug sales, and ivermectin is also not an exception[66]. Fortunately, the ivermectin has a high therapeutic margin, the adverse effects encountered are comparatively less.

Despite vigorous study of existing literature, we are still unsure of

dosage and duration of administration of ivermectin. Considering the shortcomings (duly mentioned in forestplots and Table 2), we also propose the evidence of lowcertainty for the use of ivermectin as an add-on in management and prophylaxis of COVID-19 illness.

Authors have tried to make a valid comparison by establishing uniform endpoints from the existing literature. The standard care was defined in many studies as per their local guidelines; standard care is not the same in each study. The availability of a fewer number of studies is another limitation. We have not assessed the effects of co-morbidities on the outcome of COVID-19. A majority of studies involved patients of mild to moderate severity; the findings cannot be generalized. Meta-analysis of serious adverse events was not performed.

Ivermectin is still being used in many parts of world for COVID-19 without proper evidence. Authors have tried to create evidence to promote the rational use of ivermectin. Though the favorable effects of ivermectin in some endpoints have been observed, the widespread use of ivermectin should not be promoted due to the apparent limitations of the studies. More vigorous studies with an appropriate sample size are required so that a valid conclusion can be drawn.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Authors' contributions

AS and SPD planned for the study. AS and PG performed the literature search, while AS, PG, and DG performed data extraction. SPD critically evaluated the manuscript. The final manuscript approved by all the authors.

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