Role of Ivermectin in Management of COVID-19; A Systematic Review and Meta-Analysis

Review Article

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in Wuhan, China, in December 2019.

Results: We found in our systematic review that compared with SOC or placebo, IVM did not reduce primary outcomes (all-cause mortality rate and LOS) or secondary outcomes (SARS-CoV-2 clearance in respiratory samples, mild and severe adverse events) in RCTs of patients with mostly mild COVID-19 disease. The QoE was low or very low for all outcomes. Results of subgroup analyses by severity of COVID-19 disease or RoB were mostly consistent with those of the main analyses, except for a significant effect on all-cause mortality rate in 2 RCTs with significant RoB and very low QoE.

Conclusions: Compared with SOC or placebo, Ivermectin did not reduce all-cause mortality rate, LOS, respiratory viral clearance, mild adverse effects, or severe adverse effects in RCTs of patients with mild to moderate COVID-19. We did not find data about Ivermectin effects on clinical improvement or the need for mechanical ventilation. Additional ongoing RCTs should be completed to update our analyses. In the meanwhile, Ivermectin is not a viable option for treating patients with COVID-19, and should be used only within clinical trials.

Key Words: COVID 19, ivermectin, IVM, SARS COV 2.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). The first known case was identified in Wuhan, China, in December 2019[1].

The World Health Organization (WHO) declared a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on 11 March 2020. Since 2021, variants of the virus have emerged and become dominant in many countries, with the Alpha, Beta and Delta variants being the most virulent. As of 10 October 2021, more than 237 million cases and 4.85 million deaths have been confirmed, making it one of the deadliest pandemics in history[2].

Symptoms of COVID-19 are variable, but often include fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste. Symptoms may begin one to fourteen days after exposure to the virus. At least a third of people who are infected do not develop noticeable symptoms[3].

Ivermectin is a well-known medicine that is approved for use as an anti-parasitic medication, in addition to its anti-parasitic activity; it has been noted to have antiviral and anti-inflammatory properties, leading to an increasing list of therapeutic indications[4].

Since the start of the SARS-CoV-2 pandemic, both observational and randomized studies have evaluated ivermectin as a treatment for, and as prophylaxis against, COVID-19 infection. A review by the Front Line COVID-19 Critical Care Alliance (FLCCC) summarized findings from 27 studies on the effects of ivermectin for the prevention and treatment of COVID-19 infection, concluding that ivermectin "demonstrates a strong signal of therapeutic efficacy" against COVID-19[5].

Currently, ivermectin is commercially available and affordable in many countries globally. For these reasons, if demonstrated to be effective as a treatment for COVID-19, the cost-effectiveness of ivermectin should be considered against existing treatments[6].

AIM OF THE STUDY

To investigate the efficacy and safety of ivermectin in treatment of COVID-19 and solve the ongoing debate.

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PATIENTS AND METHODS

Systematic review and meta-analysis, an electronic search will be conducted from the inception till January, 2022 about management of COVID-19 pandemic and role of ivermectin, Data will be independently extracted by two reviewers and cross checked.

Our search yielded 256 citations with an additional 9 citations identified in preprint Web pages; 253 records were excluded. After assessing 12 full texts, we identified 10 RCTs (*n*= 1195) (Figure 1).

Two full texts were excluded; there was no control group in one of these studies, and an outcome of no interest (duration of fever) was the only outcome reported in the other.

Study period was From January 2021till January 2022.

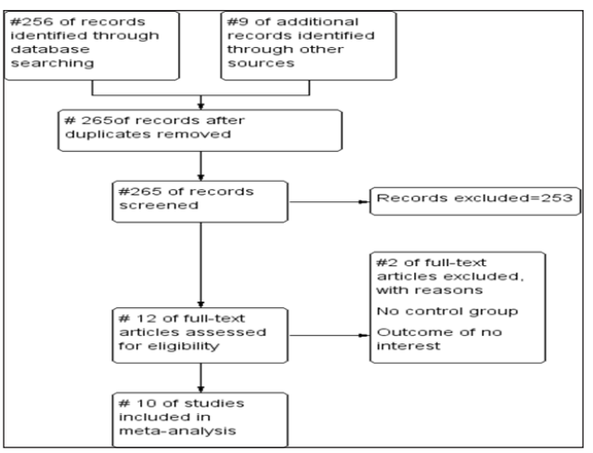

Figure 1: Study selection.

Study population

Inclusion criteria

Studies performed on Adult patients more than 18 years old, Hospitalized with Positive PCR for COVID-19, Evaluating treatment with ivermectin for SARS CoV-2 infected patients, moderate to severe cases, randomized controlled trials (RCTs) (Table 1, 2).

Exclusion criteria

Clinical trials with no control arm, those evaluating prevention of infection were excluded, Non-randomized trials, Case-control studies or studies with high risk of bias (recall bias, publication bias and lower number of participants).

Sampling methods

An electronic search will be conducted from the inception till January, 2022 using the following bibliographic databases: Medline via PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science to identify relevant articles.

The quality of the retrieved RCTs will be assessed according to the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (updated March 2011) using the quality assessment table provided in the same book (part 2, Chapter 8.5).

Sampling size

We included 10 randomized controlled trials (RCTs) with lowest risk of bias and highest evidence including 1195 patient for the total meta-analysis we excluded case-control studies and case series due to their higher risk of bias (recall bias, publication bias and lower number of participants).

Ethical considerations

We will test for publication bias using funnel plots if any of the pooled analysis included more than 5 studies in the review[7]. There is no other ethical consideration or conflicts of interest.

Study tools

Using anti parasitic ivermectin in management of COVID-19 pandemic.

Outcome measures

Ivermectin versus control in treatment of moderate to severe cases positive for COVID PCR.

Primary outcomes

Overall mortality in 30 days and Length of hospital stays in days (Figure 2, 3 and Table 3,4).

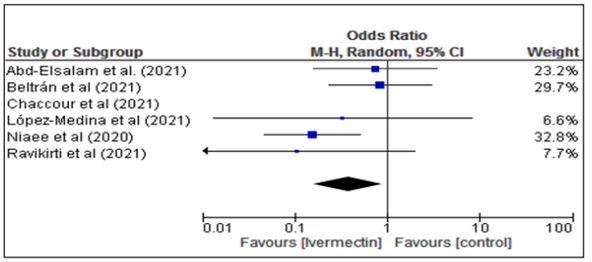

Figure 2: Forest plot for mortality.

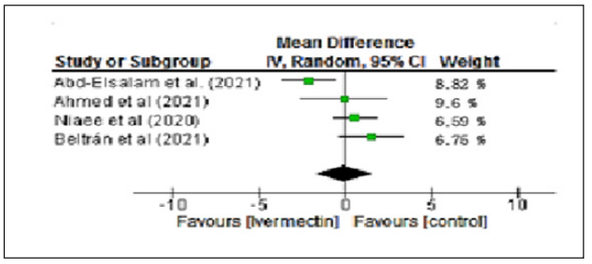

Figure 3: Forest plot for length of hospital stay.

Table 1: Baseline characteristics of studies included in meta-analysis:

Study Authors (Year)	Country (Sample Size)	IVM Dose and Duration	Control Group	COVID-19 Severity by WHO Classification	Patient Age, Mean (SD) or Median (IQR), y	RT-PCR Positive for SARS-CoV-2	Hospitalized
Abd-Elsalam *et al.,* (2021)	Egypt (*n*=164)	IVM 12mg/d oral for 3 days+SOC	SOC	Mild/moderate COVID-19 inpatients	42.38±16.02	100%	100%
Krolewiecki *et al.,* (2020)	Argentina (*n*= 45)	0.6mg/kg once daily for 5d	SOC	Mild in 87%, moderate in 13%	41(12)	100%	100%
Niaee *et al.,* (2020)	Iran (*n*= 180)	4 doses: from 200µg/kg single dose to 800µg/kg over 5d	SOC	Mild or moderate (unclear distribution)	56(45–67)	71%	100%
Podder *et al.,* (2020)	Bangladesh (*n*= 62)	Single dose: 200µg/kg	SOC	Mild in 81%, moderate in 19%	39(12)	100%	NR
Ahmed *et al.,* (2021)	Bangladesh (*n*= 48)	12mg once daily for 5d	Placebo	Mild in 100%	42(NR)	100%	100%
Beltrán-Gonzalez *et al.,* (2021)	Mexico (*n*= 73)	Single dose: 12 mg if <80kg; 18mg if >80kg	Placebo	Moderate in 74% with PaO2/FiO2 ratio 100 to 300)	53(17)	100%	100%
Chaccour *et al.,* (2020)	Spain (*n*= 24)	Single dose 400µg/kg	Placebo	Mild in 100%	26(19–36)	100%	0%
Bukhari *et al.,* (2021)	Pakistan (*n*= 86)	Single dose: 12mg	SOC	Mild in most patients (percentage unclear)	39(42)	100%	100%
López-Medina *et al.*, (2021)	Colombia (*n*= 398)	300µg/kg once daily for 5d	Placebo	Mild in 100%	37(29–48)	100%	1%
Ravikirti *et al.,* (2021)	India (*n*= 115)	12mg/d for 2d	Placebo	Mild in 79%, moderate in 21%	53(15)	Positive RT-PCR or RAT results	100%

Table 2: Sex and comorbidities:

Study Authors (Year)	Female Sex %	CVD or CHD%	DM%	HTN%	Evaluated outcomes	Duration of Follow-up, days
Abd-Elsalam *et al*., (2021)	50	NR	16	19.5	all-cause mortality, LOS, need for mech vent and safety	30
Krolewiecki *et al.,* (2020)	44	NR	16	13	Viral load at d 5, IVM plasma level	30
Niaee *et al.,* (2020)	50	NR	NR	NR	All-cause mortality rate, time until remission of symptoms, LOS	5
Podder *et al.,* (2020)	29	NR	NR	NR	Time to full recovery, viral clearance	10
Ahmed *et al.,* (2021)	54	0	0	0	Remission of symptoms, LOS, SAEs, oxygen requirement, time to viral clearance	14
Beltrán-Gonzalez *et al.,* (2021)	38	NR	34	32	All-cause mortality rate, clinical recovery, LOS, AEs, respiratory deterioration	28
Chaccour *et al.,* (2020)	50	0	0	0	All-cause mortality rate, AEs, PCR at d 7	28
Bukhari *et al.,* (2021)	15	5.8	12	14	Time to viral clearance, AEs	28
López-Medina *et al.,* (2021)	78	1.7	6	13	All-cause mortality rate, time to complete resolution, AEs, SAEs, escalation of care	21
Ravikirti *et al.,* (2021)	28	11	36	35	All-cause mortality rate, admission to ICU, requirement for MV, viral clearance at d 6	10

SOC: Standard of care; NR: Not reported.

Secondary outcomes

Effect on viral clearance as measured by study author (improvement), Mild adverse events with ivermectin use and serious adverse events with ivermectin use (Figure 4-6 and Tables 5-7).

1. Overall mortality (primary outcome):

Table 3: Meta-analysis for overall mortality:

Study or subgroup	Ivermectin		Control		Weight	Odds ratio
	events	Total	events	Total		Random effect-95%CI
Abd-Elsalam *et al*., (2021)	3	82	4	82	23.20%	0.74 [0.16, 3.42]
Beltrán-Gonzalez *et al.,* (2021)	5	36	6	37	29.70%	0.83 [0.23, 3.02]
Chaccour *et al.,* (2020)	0	12	0	12		Not estimable
López-Medina *et al.,* (2021)	0	200	1	198	6.60%	0.33 [0.01, 8.11]
Niaee *et al.,* (2020)	4	120	11	60	32.80%	0.15 [0.05, 0.51]
Ravikirti *et al.,* (2021)	0	57	4	58	7.70%	0.11 [0.01, 2.00]
Total (95% CI)		507		447	100.00%	0.37 [0.16, 0.88]
Total events	12		26			
Heterogeneity: Tau^2= 0.21; Chi^2= 5.14, df= 4 (*P*= 0.27); I^2= 22%						
Test for overall effect: Z= 2.26 (*P*= 0.02)						

IVM: Compared with control treatment, have significant effect on the all-cause.

2. Length of hospital stays in days:

Table 4: Meta-analysis for Length of hospital stays in days:

STUDY OR SUBGROUP	Ivermectin			Control			Weight	Mean difference
	Mean	SD	Total	Mean	SD	Total		IV-Random 95%CI
Abd-Elsalam *et al*., (2021)	8.82	4.94	82	10.97	5.28	82	8.82	-2.15 [-3.72, -0.58]
Ahmed *et al.,* (2021)	9.6	4.75	24	9.7	4.0	24	9.6	-0.10 [-2.58, 2.38]
Beltrán *et al.,* (2021)	6.75	5.19	36	5.25	2.22	37	6.75	1.50 [-0.34, 3.34]
Niaee *et al.,* (2020)	6.59	2.47	116	6.02	4.05	49	6.59	0.57 [-0.65, 1.79]
Total (95% CI)			258			192	100.00%	-0.06 [-1.66, 1.55]
Heterogeneity: Tau^2= 1.87; Chi^2= 10.64, df= 3(*P*= 0.01); I^2= 72%								
Test for overall effect: Z= 0.07 (*P*= 0.94)								

IVM: Compared with control treatment, did not have significant effect on the LOS rate in 6 RCTs due to high degree of heterogeneity (OR, -0.06 [-1.66, 1.55]); I2= 72% *P* value= .01 very low QoE.

3-Effect on viral clearance:

Table 5: Meta-analysis for effect on viral clearance:

Study or subgroup	Ivermectin		Control		weight	Odds ratio
	events	Total	events	Total		Random effect-95%CI
Bukhari *et al.,* (2021)	18	20	19	20	5.50%	0.47 [0.04, 5.69]
Chaccour *et al.,* (2020)	0	12	0	12		Not estimable
Podder *et al.,* (2020)	20	41	18	45	46.20%	1.43 [0.61, 3.36]
Ravikirti *et al.,* (2021)	13	55	18	57	48.30%	0.67 [0.29, 1.55]
Total (95% CI)		128		134	100%	0.93 [0.52, 1.67]
Total events	51		55			
Heterogeneity: Tau^2= 0.00; Chi^2= 1.84, df= 2 (*P*= 0.40); I^2= 0%						
Test for overall effect: Z= 0.23 (*P*= 0.82)						

IVM: Compared with control treatment, did not have significant effect on the effect on viral clearance in 4 RCT (OR 0.93 [0.52, 1.67]); I^2= 0% but *P*= 0.82 very low QoE.

4-Effect on mild adverse events:

Table 6: Meta-analysis for effect on mild adverse events:

study or subgroup	Ivermectin		Control		weight	Odds ratio Random effect-95% CI
	events	total	events	Total		
Chaccour *et al.,* (2021)	5	12	5	12	7.30%	1.00 [0.20, 5.07]
Krolewiecki *et al.,* (2020)	13	30	5	15	11.50%	1.53 [0.42, 5.58]
López-Medina *et al.,* (2021)	154	200	161	198	81.30%	0.77 [0.47, 1.25]
Total (95% CI)		242		225	100.00%	0.85 [0.55, 1.31]
Total events	172		171			
Heterogeneity: Tau²= 0.00; Chi²= 0.99, df= 2(*P*= 0.61); I²= 0%						
Test for overall effect: Z= 0.74 (*P*= 0.46)						

IVM: Compared with control treatment, did not have significant effect on mild adverse events in 4 RCT (OR 0.85 [0.55, 1.31]); I²= 0% but *P*= 0.4 low QoE.

5-Effect on severe adverse events:

Table 7: Meta-analysis for effect on severe adverse events:

study or subgroup	Ivermectin		Control		Weight	Odds ratio
	events	total	events	Total		Random effect-95% CI
Abd-Elsalam *et al*., (2021)	0	24	0	24		Not estimable
Ahmed *et al.,* (2021)	0	41	0	45		Not estimable
Bukhari *et al.,* (2021)	1	30	0	15	20.00%	1.58 [0.06, 41.03]
Krolewiecki *et al.,* (2020)	3	82	3	82	80.00%	1.00 [0.20, 5.11]
Total (95% CI)		177		166	100.00%	1.10 [0.25, 4.71]
Total events	4		3			
Heterogeneity: Tau²= 0.00; Chi²= 0.06, df= 1(*P*= 0.81); I²= 0%						
Test for overall effect: Z= 0.12 (*P*= 0.90)						

IVM: compared with control treatment, had no effect on severe adverse events in 4 RCT (OR 1.10 [0.25, 4.71]); I²= 0% but *P*= 0.81 low QoE.

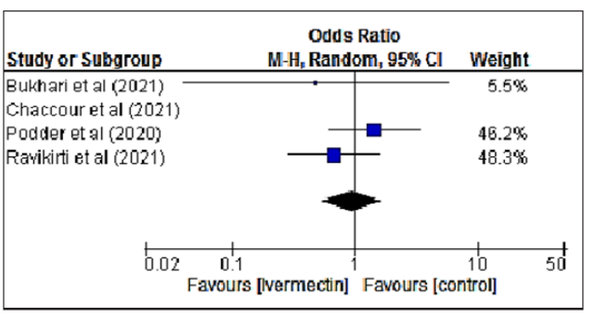

Figure 4: Forest plot for effect on viral clearance.

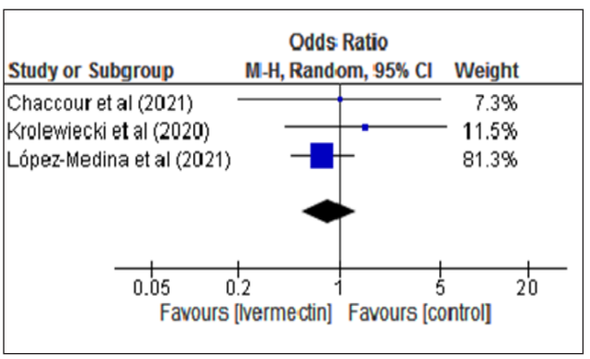

Figure 5: Forest plot for effect on mild adverse events.

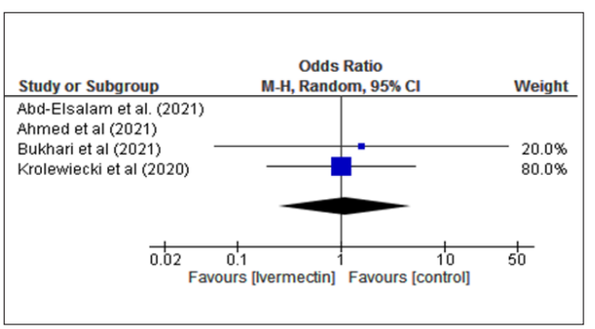

Figure 6: Forest plot for severe adverse events.

Statistical analysis

Meta-analysis will be performed using Review Manager (RevMan) software version 5.4 for meta-analysis. In case of continuous outcomes Mean±SD and total sample count will be collected then the mean differences were pooled to calculate the weighted mean with 95% confidence intervals (CIs), while in case of dichotomous outcomes, frequencies and total sample count will be collected then the relative rates will be pooled to calculate the weighted relative rate with its 95% confidence intervals (CIs). Forest plots will be used to present the individual and weighted estimates. Heterogeneity index will be calculated

to test variation of pooled estimates for each outcome, and presented by Funnel plot. The level of significance was taken at *P* value <0.050 is significant, otherwise_is_non_ significant.

Characteristics of RCTs

One RCT was conducted in Spain[6], One in Egypt[8] and the other eight were conducted in low- and middle-income countries. Sample sizes for RCTs ranged from 24[6] to 398[9] patients. IVM doses were heterogeneous in terms of total doses ranging from 12mg[10] to 210mg[11].

Risk of bias

We assessed the risk of bias (RoB) using the Cochrane Risk of Bias 2.0 tool for RCTs[12]; disagreements were resolved by discussion This tool evaluates 5 domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The RoB for each of the 5 domains and overall was described as low, some concerns, or high.

DISCUSSION

We found in our systematic review that compared with SOC or placebo, IVM did not reduce primary outcomes (all-cause mortality rate, LOS, and AEs) or secondary outcomes (SARS-CoV-2 clearance in respiratory samples, and SAEs) in RCTs of patients with mostly mild COVID-19 disease. The QoE was low or very low for all outcomes. Results of subgroup analyses by severity of COVID-19 disease or RoB were mostly consistent with those of the main analyses, except for a significant effect on all-cause mortality rate in 2 RCTs with significant RoB and very low QoE. Two conventional systematic review and meta-analyses and 2 living systematic review and meta-analyses were published. Padhy *et al.,* published the first systematic review about IVM in patients with COVID-19, and their primary outcome was all-cause mortality rate. This study included only 4 observational studies (*n*= 629). IVM showed reduction of all-cause mortality rate (odds ratio [OR], 0.53 [95% CI, .09–.36]). However, the authors express caution as the QoE was very low[13].

RoB in most of the RCTs, described their findings as preliminary, and suggested that IVM should preferably be administered within RCTs[14].

Siemieniuk *et al.,* published a living systematic review of Ivermectin in patients with COVID-19, with mortality rate as the primary outcome and 10 other outcomes, including hospitalization and time to viral clearance .Seven RCTs contributed to the mortality assessment (*n*= 751). Ivermectin was associated with a reduced mortality rate (risk difference per 1000 vs SOC, −103 [95% CI, −117 to −78]), but the QoE was very low[15].

Taken together, the results of these 4 studies suggested that IVM should not be used in patients with COVID-19. Living systematic reviews allow authors to update the evidence regularly, which is particularly important in a pandemic scenario[16].

We also found 3 preprints of systematic reviews: Castaneda-Sabogal *et al.,* evaluated 12 studies (6 RCTs, 5 retrospective cohorts, and 1 case series; *n*= 7412) without description of COVID-19 severity. IVM did not reduce the mortality rate (RR, 0.70 [95% CI, .31–2.28]) or increase the rate of recovery (1.37 [.61–3.07]). The authors concluded that there was insufficient certainty and low QoE[17].

Finally, Andrew *et al.,* evaluated 19 RCTs (*n*= 2003). In 13 of the 19 (3 published RCTs, 9 preprints, and 1 trial registry Web registry; *n*= 1892) with mostly mild to moderate disease severity, IVM reduced the mortality rate (adjusted RR, 0.32 [95% CI, .14–.72]); the QoE was low to moderate. Andrew *et al.,* recommended the use of IVM in COVID-19, particularly in early disease, without supporting data[18].

Ivermectin is generally safe at conventional doses for approved indications. However, its safety became a concern owing to longer use and higher doses in patients with COVID-19. IVM was found to be similar to placebo in safety and tolerability, even at 10 times the highest FDA-approved dose of 200μg/kg in healthy volunteers, but not in patients with COVID-19. In addition, the use of IVM needs further analysis when IVM is combined with other agents for COVID-19[19].

Our study has several strengths. First, we performed a recent and comprehensive systematic search in 5 engines and unpublished studies without language restriction. Second, we evaluated only RCTs; several previous studies included all types of designs, and their findings may have been biased and confounded. Third, we evaluated outcomes with information from at least 2 RCTs. Fourth, we described the severity of COVID-19 disease in each RCT carefully, using the WHO classification[5]; our findings do not support the use of IVM in mild disease. Fifth, we performed subgroup analyses by RoB and severity of disease, the results of which were mostly similar to those of the main analyses; however, we found that RCTs with a high RoB had significant reductions in all-cause mortality rates. Sixth, we also performed sensitivity analysis by excluding studies with short follow-up times; the effects were similar. Finally, we evaluated the QoE using GRADE methods.

Our study also has some limitations. First, the QoE was low or very low for all outcomes. However, our study evaluated the best current available evidence, and all IVM effects were negative. Second, we included only 10 RCTs,

5 of which used placebo treatment as the control, and studies included relatively small numbers of participants. However, included RCTs are the studies available through study period. Third, all selected RCTs evaluated patients with mild or mild to moderate COVID-19. However, the supposed benefit of IVM has been positioned precisely for mild disease, but we did not find differential Ivermectin effects between these 2 severity categories. Fourth, some outcomes were scarce, in particular all-cause mortality rates and SAEs; we adjusted for zero events in one or both RCT arms in our analyses of these outcomes. Finally, analyses of primary outcomes excluding studies with short follow-up (5–10 days) showed similar IVM effects.

CONCLUSION

Compared with Standard of care or placebo, Ivermectin did not reduce all-cause mortality rate, Length of stay (LOS), respiratory viral clearance, mild adverse effects, or severe adverse effects in RCTs of patients with mild to moderate COVID-19. We did not find data about Ivermectin effects on clinical improvement or the need for mechanical ventilation. Additional ongoing RCTs should be completed to update our analyses. In the meanwhile, Ivermectin is not a viable option for treating patients with COVID-19, and should be used only within clinical trials.

ABBREVIATIONS

AEs: Adverse events, **Cis:** Confidence intervals, **COVID-19:** Coronavirus disease 2019, **FLCCC:** Front Line COVID-19 Critical Care Alliance, **IVM:** Ivermectin, **LOS:** Length of stay, **NR:** Not reported, **PCR:** Polymerase chain reaction, **QOE:** Quality of evidence, **RCT:** Randomized controlled trial, **ROB:** Risk of bias, **SAEs:** Serious adverse events, **SARS:** severe acute respiratory syndrome, **SARS-CoV-2:** Severe acute respiratory syndrome coronavirus 2, **S D:** standard deviation, **SOC:** Standard of care, **WHO:** World Health Organization.

AUTHORS' CONTRIBUTIONS

Hanna El-Gendy: Designed the study, reviewed manuscript. Heba Ahmed: participated in study design, data interpretation. Amal Rabie: participated in study design. Wael Omran: assisted with manuscript preparation, data collection and interpretation. Bahaa El din Hassan: wrote manuscript & figures preparation, collected, analyzed and interpreted the data. All authors reviewed the manuscript.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The authors declare that they have no conflicts of interest, no ethical consideration. Consent to participate: Not applicable as this study is systematic review and meta-analysis.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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