Ivermectin for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials

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Summary: Our systematic review of randomized controlled trials showed that ivermectin did not reduce all-cause mortality, length of stay or viral clearance vs. controls in COVID-19 patients with mostly mild disease. Ivermectin is not a viable option to treat COVID-19 patients.

Abstract

Background: We systematically assessed benefits and harms of the use of ivermectin (IVM) in COVID-19 patients.

Methods: Published and preprint randomized controlled trials (RCTs) assessing IVM effects on COVID-19 adult patients were searched until March 22, 2021 in five engines. Primary outcomes were all-cause mortality, length of stay (LOS), and adverse events (AE). Secondary outcomes included viral clearance and severe AEs. Risk of bias (RoB) was evaluated using Cochrane RoB 2·0 tool. Inverse variance random effect meta-analyses were performed. with quality of evidence (QoE) evaluated using GRADE methodology.

Results: Ten RCTs (n=1173) were included. Controls were standard of care [SOC] in five RCTs and placebo in five RCTs. COVID-19 disease severity was mild in 8 RCTs, moderate in one RCT, and mild and moderate in one RCT. IVM did not reduce all-cause mortality vs. controls (RR 0.37, 95%CI 0.12 to 1.13, very low QoE) or LOS vs. controls (MD 0.72 days, 95%CI −0.86 to 2.29, very low QoE). AEs, severe AE and viral clearance were similar between IVM and controls (all outcomes: low QoE). Subgroups by severity of COVID-19 or RoB were mostly consistent with main analyses; all-cause mortality in three RCTs at high RoB was reduced with IVM.

Conclusions: In comparison to SOC or placebo, IVM did not reduce all-cause mortality, length of stay or viral clearance in RCTs in COVID-19 patients with mostly mild disease. IVM did not have an effect on AEs or severe AEs. IVM is not a viable option to treat COVID-19 patients.

Keywords: Ivermectin; SARS-CoV-2; COVID-19; mortality; meta-analysis.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic represents a global sanitary, social and economic challenge. However, scientific advances have also amplified deficiencies and misinformation [1]. Biological plausibility, pathophysiological considerations, *in vitro* research, observational studies, and/or clinical trials with heterogeneous quality evaluated several repurposed drugs different from their current indications. Some policy-makers and regulatory institutions authorized emergency use of unproven COVID-19 treatments; the use of some of these treatments has been heavily politicized in some regions [2, 3].

Ivermectin (IVM) is a semisynthetic, anthelmintic agent for oral administration, and derived from the avermectins of *Streptomyces avermitilis*. IVM and its analogs selectively open inhibitory glutamate-gated chloride ion channels in the cell membranes of nematodes. In addition, IVM prevents the filarial ability to release inhibitors of the host immune response [4]. In tissue cultures, at concentrations higher than anthelmintic concentrations, IVM showed antiviral (e.g., dengue), antiparasitic (e.g., malaria), and anticancer (e.g., epithelial ovarian cancer) effects. However, these *in vitro* results have not been clinically demonstrated [4].

In March 2020, researchers from Australia showed IVM to be active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures by drastically reducing viral RNA at 48 hours [5]. Concentrations were equivalent to more than 50-fold the normal C_{max} achieved with a standard single dose of IVM 200 μg/kg, raising concerns about the efficacious dose of IVM for treating or preventing SARS-CoV-2 infection in humans and its tolerability [6]. However, theoretical considerations, experimental and observational evidence, misinformation, self-medication, and the wide availability of IVM led to its use as treatment of COVID-19 in low- and middle-income countries, assuming *a priori* efficacy and safety.

Ivermectin is currently approved by the Food and Drug Administration (FDA) to treat people with intestinal strongyloidiasis and onchocerciasis. The European Medicines Agency [7] and FDA [8] have not approved IVM for the treatment of COVID-19. World Health Organization (WHO) [9] and Infectious Diseases Society of America (IDSA) [10] guidelines, do not recommend IVM for treatment of COVID-19 outside randomized controlled trials (RCTs).

Three systematic reviews on the effect of IVM on clinical outcomes were published [11-13]. Padhy et al. only included three small observational studies [11]. Siemieniuk et al. conducted a living systematic review of all treatments for COVID-19, but details were scarce and quality of evidence was very low [12]. Finally, Kow et al. evaluated six RCTs, five of them from Asia and none from Latin America [13]. Other systematic reviews or narrative reviews of IVM effects only have been disseminated as pre-prints [14-16] or on websites [17-19].

We conducted a systematic review and meta-analysis to evaluate treatment effects of IVM on clinical outcomes and adverse events in people with COVID-19.

Methods

Sources and Searches

Two investigators (VP, and AVH) developed the search strategy, which was approved by the other investigators. Until March 22, 2021, we searched five databases: PubMed-MEDLINE, EMBASE-OVID, Scopus, Web of Science, the Cochrane Library; and preprints from www.medrxiv.org, www.preprints.org, and www.ssrn.com. The PubMed search strategy is shown in the **Supplement**.

Selection of studies

We included RCTs in any language reporting benefit or harm outcomes of IVM as treatment in COVID-19 patients, both non-hospitalized and hospitalized, irrespective of COVID-19 severity. We excluded studies assessing prophylaxis for COVID-19 infection. Controls were standard of care (SOC) or placebo. Two investigators (YMR, AB) independently screened titles and abstracts, and then assessed full texts of selected abstracts. Discrepancies were resolved through discussion or by a third investigator (AVH).

Outcomes

Primary outcomes were all-cause mortality, length of hospital stay, and adverse events (AE). Secondary outcomes were SARS-CoV-2 clearance on respiratory samples, clinical improvement, need for mechanical ventilation, and severe adverse events (SAE). AEs and SAEs were extracted as defined by authors.

Data Extraction

Two investigators (YMR and AB) independently extracted: country(ies), sample size, dose and duration of IVM treatment, type of control group (SOC vs. placebo), COVID-19 severity, percentage of positive reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2, study setting (hospitalized vs. non-hospitalized), mean age, proportion of female, hypertension, diabetes mellitus and cardiovascular disease, outcomes, and time of follow up. COVID-19 disease severity was defined as mild, moderate or severe according to the WHO classification [20]. Discrepancies were resolved through discussion or by two other investigators (AP, AVH).

Risk of bias assessment

Two investigators (YMR and AB) independently assessed risk of bias (RoB) by using the Cochrane Risk of Bias 2.0 tool for RCTs [21]; disagreements were resolved by discussion with a third investigator (AP). The RoB 2.0 tool evaluates five domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. RoB per each of the five domains and overall were described as low, some concerns and high.

Statistical analyses

We reported our systematic review according to 2009 PRISMA guidelines [22]. Inverse variance random effect meta-analyses were performed to evaluate effect of IVM vs. control on outcomes. Effects of meta-analyses were reported as relative risks (RR) for dichotomous outcomes and as mean difference (MD) for continuous outcomes. The between study variance tau^2 was calculated with the Paule-Mandel method [23] and the 95% confidence intervals (CIs) of effects were adjusted with the Hartung-Knapp method [24]. We adjusted for zero events in one or two RCT arms using the continuity correction method [25]. Heterogeneity of effects among studies was quantified with the I^2 statistic (I^2>60% means high heterogeneity). We pre-specified subgroup analyses by severity of COVID-19 disease and RoB; the p for interaction test <0.1 indicated effect modification by subgroup. Sensitivity analyses by excluding RCTs with shorter follow-up (i.e. <21 days) were planned for the primary outcomes. The *meta* package of R 3.5.1 (www.r-project.org) was used for meta-analyses. The quality of evidence (QoE) was evaluated using GRADE methodology, which covers: risk of bias, inconsistency, indirectness, imprecision, and publication bias [26]. QoE was evaluated per outcome, and described in summary of findings (SoF) tables; GRADEpro GDT was used to create SoF tables [27].

Results

Selection of studies

Our search yielded 256 citations with an additional nine citations identified in pre-print web pages; 253 records were excluded. After assessing 12 full-texts, we identified 10 RCTs [28-37] (n=1,173) (**Figure 1**). Two full-texts were excluded as there was no control group in one study, and an outcome of no interest (duration of fever) was the only one reported in another study.

Characteristics of RCTs

One RCT was conducted in Spain [34] and the other nine RCTs in low- and middle-income countries. Sample sizes of RCTs ranged from 24 [34] to 398 [36] patients. IVM doses were heterogeneous in terms of total doses (12mg [35] to 210 mg [29]) and duration (one [28, 31, 33-35] to five [29, 30, 32, 36] days). Controls were SOC in five RCTs [28-31, 35] and placebo in five RCTs [32-34, 36, 37]. Most of RCTs were conducted in mild COVID-19 patients: mild in all or the majority of patients in eight RCTs [28, 29, 31, 32, 34-37], moderate in one RCT [33], and mild and moderate in one RCT [30] (**Table 1**).

All patients had positive RT-PCR for SARS-CoV-2 at baseline, except in 2 RCTs: Niaee et al. [30] had 71% positivity, and Ravikirti et al. [37] had positive RT-PCR or rapid antigen test. The RCTs by Chachar et al. [28], Chaccour et al. [34], and López-Medina et al. [36] were conducted in non-hospitalized patients. Mean/median age ranged from 26 to 56 years-old, the percentage of females ranged from 15% [35] to 78% [36], and most of patients did not have hypertension, diabetes or cardiovascular disease. Evaluated outcomes were also heterogeneous across RCTs, and time of follow up ranged from five [29) to 30 days [29].

Risk of bias assessment of included RCTs

Eight RCTs were at high RoB [28-32, 35-37], Beltran et al. [33] had some concerns of bias in the randomization process, and Chaccour et al. [34] was at low RoB (**see Supplementary Figure 1** for details).

Meta-analyses

IVM did not have effect on all-cause mortality vs. controls in five RCTs (RR 0.37, 95%CI 0.12 to 1.13, I^2=16%, very low QoE) (**Figure 2, Table 2**), on length of stay vs. controls in three RCTs (MD 0.72 days, 95%CI -0.86 to 2.29, I^2=0%, very low QoE) (**Figure 3, Table 2**), and on adverse events vs. controls in three RCTs (RR 0.95, 95%CI 0.85 to 1.07, I^2=0%, low QoE) (**Figure 4, Table 2**).

There was no effect of IVM on severe adverse events in comparison to the controls in three RCTs (RR 1.39, 95%CI 0.36 to 5.30, I^2=0%, low QoE) (**Figure 5, Table 2**) and on viral clearance in comparison to the controls in four RCTs (RR 0.96, 95%CI 0.79 to 1.16, I^2=0%, low QoE) (**Figure 6, Table 2**).

Subgroup and sensitivity analyses

Subgroup analyses by severity of COVID-19 disease or RoB were consistent with main analyses (**see Supplementary Figures 2.1 to 2.5**), except the subgroup by RoB of all-cause mortality; three studies [30, 36, 37] at high risk of bias showed a significant reduction in all-cause mortality (RR 0.18, 95%CI 0.07-0.49; RoB p for interaction=0.1). Sensitivity analyses excluding studies with follow-up <21 days showed similar effects as primary analyses for all-cause mortality and length of stay (**see Supplementary Figures 3.1 and 3.2**). Statistical heterogeneity of effects for all-cause mortality was 0% in sensitivity analysis.

Discussion

We found in our systematic review that in comparison to SOC or placebo, IVM did not reduce primary outcomes (all-cause mortality, length of hospital stay, and adverse events) or secondary outcomes (SARS-CoV-2 clearance in respiratory samples, and severe adverse events) in RCTs of patients with mostly mild COVID-19 disease. The quality of evidence was low or very low for all outcomes. Subgroup analyses by severity of COVID-19 disease or risk of bias were mostly consistent with main analyses, except a significant effect on all-cause mortality in three RCTs at high risk of bias.

Two conventional systematic review and meta-analyses and two living systematic review and meta-analyses were published [9, 11-13] (**see Supplementary Table 1**). Padhy et al. published the first systematic review about IVM in COVID-19 patients and their primary outcome was all-cause mortality [11]. This study included only four observational studies (n=629). IVM showed reduction of all-cause mortality (OR 0.53, 95%CI 0.09-0.36). However, the authors claim caution as the quality of evidence was very low [11]. Kow et al. published a systematic review of IVM effects in COVID-19 patients on all-cause mortality [13]. This study included only 6 RCTs (n=1255). IVM showed reduction of all-cause mortality (OR 0.21, 95%CI 0.11-0.42).The authors showed high risk of bias in the most of the RCTs, described their findings as preliminary, and suggested IVM should preferably be administered under RCT settings [13].

The WHO published a living systematic review about IVM in COVID-19 patients with all-cause mortality as primary outcome [9]. Sixteen RCTs were evaluated, but only five directly compared IVM with SOC and reported mortality (n=915); IVM reduced all-cause mortality (OR 0.19, 95%CI 0.09-0.36). However, QoE was very low for mortality and the panel concluded that the effect of IVM on mortality was uncertain. Other outcomes (i.e. mechanical ventilation, hospital admission, and duration of hospitalization) also had very low

QoE. WHO only recommended using IVM in RCTs [9]. Siemieniuk et al. published a living systematic review about IVM in COVID-19 patients with mortality as primary outcome and other ten outcomes including hospitalization, and time to viral clearance [12]. Seven RCTs contributed to mortality assessment (n=751). IVM showed reduction of mortality (Risk difference per 1000 vs. SOC: -103, 95%CI -117 to -78), but the QoE was very low. For other critical outcomes the QoE was low. This study concluded that effects of IVM were highly uncertain, without definitive evidence of important benefits and harms [12]. Taken together, the results of these four studies suggested that IVM should not be used in COVID-19 patients. Living systematic reviews allow authors to update the evidence regularly, which is particularly important in a pandemic scenario [38].

We also found three pre-prints of systematic reviews [14-16] (**see Supplementary Table 2**). Castañeda-Sabogal et al. evaluated 12 studies (six RCTs, five retrospective cohorts, and one case series; n=7412), without description of COVID-19 severity. IVM did not reduce mortality (RR 0.70, 95%CI 0.31-2.28) and did not increase recovery (RR 1.37, 95%CI 0.61 to 3.07). Authors concluded that there was insufficient certainty and low QoE [14]. Hill et al. evaluated 18 RCTs (n=2282) with mostly mild to moderate severity. In six RCTs (four pre-prints and two trial registry web records; n=1255), IVM reduced all-cause mortality (RR 0.25, 95%CI 0.12 to 0.52) but did not increase recovery (RR 1.37, 95%CI 0.61-3.07). The RCT quality was classified as limited in four, fair in one, and good in one study. These authors concluded that IVM should be evaluated in well-designed, large RCTs [15]. Finally, Bryant et al. evaluated 19 RCTs (n=2003). In thirteen RCTs (three published RCTs, nine pre-prints, and one trial registry web registry; n=1892) with mostly mild to moderate severity, IVM reduced mortality (adjusted RR 0.32, 95%CI 0.14 to 0.72) [16]; QoE was of low to moderate. Authors recommended the use of IVM in COVID-19, in particular in early disease without supporting data. The last two studies [15, 16] used very flexible research strategies

and included 0% and 13% of peer-reviewed studies, respectively. In consequence, they were subject to selection bias that may explain IVM effects on mortality.

Several websites published systematic reviews and meta-analyses about IVM in COVID-19 patients with unclear or absent methodology and reporting guidelines [17-19] (**see Supplementary Table 2**). These websites did not include protocol registration and have relevant omissions such as inclusion criteria [19], searched databases [18, 19], study quality assessment [17, 19], meta-analysis methods [19], and heterogeneity definition [17, 19]. Arbitrarily broad inclusion criteria (i.e. studies directly submitted to the websites, more pre-prints than peer-review studies) led to a high number of RCTs and participants. For example, a "real time meta-analysis" ivmmeta.com included 46 studies, 24 of them RCTs, and 15,480 participants [17]. Coincidentally, these three studies showed beneficial outcome effects with IVM [17-19]. In a context of misinformation infodemic, the dissemination of these results caused confusion for patients, clinicians (in particular those without training in critical reading of scientific literature), and decision-makers, who may manipulate the information with political interests [39].

The non-rational use of IVM to treat COVID-19 patients has shown several limitations in management strategies: absence of transparency by some political leaders or media in order to avoid drug use without evidence of efficacy and safety; lack of leadership to implementing therapeutic science-based guidelines; and misuse of effective scientific communication [40, 41]. Similar issues were previously experienced with hydroxychloroquine and probably will be repeated with other repurposed drugs. Therefore, there is an urgent need to establish collaborative efforts among scientists, practitioners, communicators, and policy-makers. A large, well-designed and -reported RCT provides the most reliable information of efficacy in the specific target population from which the sample

was drawn. Well-designed and reported meta-analyses can provide valuable and confirmatory information [42].

Ivermectin is generally safe at the conventional doses in approved indications [4, 5]. However, IVM safety became a concern due to longer use and/or higher doses in COVID-19 patients. IVM was found to be of similar safety and tolerability to placebo even at 10 times the highest FDA-approved dose of 200 μg/kg in healthy voluntaries [43], but not in COVID-19 patients. In addition, IVM use needs further analysis when combined with other agents for COVID-19 [44, 45]. In several settings, it was wrongly assumed that the potential benefit of using repurposed drugs outweigh their potential harm [46]. Well-designed RCTs with longer IVM use and higher IVM doses are necessary in COVID-19 to further evaluate is safety.

Our study has several strengths. First, we performed a recent and comprehensive systematic search in five engines and unpublished studies without language restriction. Second, we only evaluated 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 two RCTs; no data was available for clinical improvement and need for mechanical ventilation. Fourth, we described the severity of COVID-19 disease per RCT carefully, using the WHO classification [19]; our findings do not support the use of IVM in mild disease. Fifth, we performed subgroup analyses by RoB and severity of disease, which were mostly similar to main analyses; however, we found that three RCTs at high risk of bias [30, 36, 37] had a significant reduction of all-case mortality. Sixth, we also performed sensitivity analysis by excluding studies with short follow up times; effects were similar. Finally, we evaluated the quality of evidence using GRADE methodology.

Our study also has some limitations. First, quality of evidence 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 ten RCTs, five of them using a placebo as

control group, and studies included a relative low number of participants. However, included RCTs are the available studies until March 22, 2021. 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 IVM effects between these two severity categories. Fourth, some outcomes were scarce, in particular all-cause mortality and severe adverse events; we adjusted for zero events in one or both RCT arms in our analyses of these outcomes. Finally, analyses of primary outcomes excluding short follow up studies (5-10 days) showed similar IVM effects.

In conclusion, in comparison to SOC or placebo, IVM did not reduce all-cause mortality, length of stay, respiratory viral clearance, adverse events and serious adverse events in RCTs of patients with mild to moderate COVID-19. We did not find data about IVM effects on clinical improvement and need for mechanical ventilation. Additional ongoing RCTs should be completed in order to update our analyses. In the meanwhile, IVM is not a viable option to treat COVID-19 patients, and only should be used within clinical trials context.

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References

1. Anonymous. Science during COVID-19: where do we go from here. Lancet, **2021**; 396(10267): 1941.
2. Saag **MS. Misguided Use of Hydroxychloroquine for COVID-19. The infusion of Politics Into Science. JAMA, 2020; 324(21): 2161-2162.**
3. Barberia LG, Gómez EJ. Political and institutional perils of Brazil's COVID-19 crisis. Lancet, **2020**; 396(10248): 367-368.
4. Martin RJ, Robertson AP, Choudhary S. Ivermectin: An Anthelmintic, an Insecticide, and Much More. TrendsParasitol, **2021**; 37(1): 48-64.
5. Chaccour C, Hammann F, Ramón-García S, Rabinovich NR. Ivermectin and Novel Coronavirus Disease (COVID-19): Keeping Rigor in Times of Urgency.*Am J Trop* Med Hyg, **2020**; 102(6):1156-1157.
6. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*. Antiviral Res, **2020**; 178: 104787.
7. European Medicines Agency. EMA advises against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials. Published 22 March 2021. Accessed 23 March 2021. https://www.ema.europa.eu/en/news/ema-advises-against-use-ivermectin-prevention-treatment-covid-19-outside-randomised-clinical-trials
8. U.S. Food and Drug Administration. Why you should not use ivermectin to Treat or Prevent COVID-19? Published 3 May 2021. Accessed 5 May 2021. https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19.

9. World Health Organization. *Therapeutics and COVID-19: living guideline*. WHO reference number: WHO/2019-nCoV/therapeutics/2021.
10. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America **2021**; Version 4.2.0. Published 14 April 2021. Accessed 15 April 2021. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.
11. Padhy BM, Mohanty RR, Das S, Meher BR. Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis. *J Pharm* Pharm Sci, **2020**; 23:462-469.
12. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ, **2020**; 370: m2980.
13. Kow CS, Merchant HA, Mustafa ZU, Hasan SS. The association between the use of ivermectin and mortality in patients with COVID-19: a meta-analysis. Pharmacol Rep. **2021**;1-7.
14. Castañeda-Sabogal A, Chambergo-Michilot D, Toro-Huamanchumo CJ, et al. Outcomes of Ivermectin in the treatment of COVID-19: a systematic review and meta-analysis. 27 January 2021. medRxiv preprint. DOI: 10.1101/2021.01.26.21250420.
15. Hill A; International Ivermectin Project Team. Preliminary meta-analysis of randomized trials of ivermectin to treat SARSCoV-2 infection. medRxiv preprint. 19 Jan 2021. DOI: 10.21203/rs.3.rs-148845/v1.
16. Bryant A, Lawrie TA, Dowswell T, et al. Ivermectin for Prevention and Treatment of COVID-19 Infection: a Systematic Review and Meta-analysis. ResearchSquare preprint. 18 March 2021.DOI: https://doi.org/10.21203/rs.3.rs-317485/v1

17. Ivermectin for COVID-19: real-time meta-analysis of 54 studies. https://ivmmeta.com. Published 8 May 2021. Accessed 9 May 2021.
18. Lawrie T. Ivermectin reduces the risk of death from COVID-19 -a rapid review and meta-analysis in support of the recommendation of the Front Line COVID-19 Critical Care Alliance. Published5 January 2021. Accessed 8 May 2021. DOI: 10.13140/RG.2.2.27751.88486.
19. Kory P, Meduri GU, Iglesias J, et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. FLCCC Alliance. Published 16 January 2021. Accessed 8 May 2021.https://covid19criticalcare.com.
20. WHO Working Group on the Clinical Characterization and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis, **2020**; 20(8):e192-e197.
21. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, **2019**; 366:l4898.
22. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med**,** **2009**; 6(7):e1000097.
23. Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to Estimate the between-Study Variance and Its Uncertainty in Meta- Analysis.*Res* Synth Methods**, 2015**; 7(1):55-79.
24. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. Stat Med, **2001**; 20(24):3875-3889.
25. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med, **2004**; 23: 1351-1375.

26. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol, **2011**; 64(4):401-406.
27. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). Accessed 7 May 2021. www.gradepro.org.
28. Chachar AZK, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of Ivermectin in SARS-CoV-2/COVID-19 Patients. Int J Sci, **2020**; 9(09):31-35.
29. Krolewiecki A, Lifschitz A, Moragas M, et al. Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19: A Pilot Randomized, Controlled, Open Label, Multicentre Trial. SSRN; Jan 2020. DOI:10.2139/ssrn.3714649
30. Niaee MS, Gheibi N, Namdar P, et al. Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial. ResearchSquare.24 Nov 2020. DOI:10.21203/rs.3.rs-109670/v1.
31. Podder C, Chowdhury N, Sina M, Haque W. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomized controlled study. IMC J Med Sci, **2020**; 14.
32. Ahmed S, Karim MM, Ross AG, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis, **2021**; 103:214-216.
33. Beltrán-Gonzalez JL, Gámez MG, Enciso EAM, et al. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. medRxiv. 23 Feb 2021. DOI:10.1101/2021.02.18.21252037
34. Chaccour C, Casellas A, Matteo AB-D, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe

COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine, **2021**; 32: 100720. DOI:10.1016/j.eclinm.2020.100720.

35. Karamat HSB, Asma A, Najma P, et al. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease. medRxiv. 5 Feb 2021. doi:10.1101/2021.02.02.21250840
36. López-Medina E, López P, Hurtado IC, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. JAMA, **2021**; 325(14):1426-1435.
37. Ravikirti, Roy R, Pattadar C, et al. Ivermectin as a potential treatment for mild to moderate COVID-19 – A double blind randomized placebo-controlled trial. medRxiv. 9 Jan 2021. DOI:10.1101/2021.01.05.21249310
38. Macdonald H, Loder E, Abbasi K. Living systematic reviews at The BMJ. BMJ, **2020**; 370:m2925.
39. Garegnani LI, Madrid E, Meza N. Misleading clinical evidence and systematic reviews on ivermectin for COVID-19. BMJ Evidence Based Medicine, **2021**; 1-3.
40. Al Saidi AMO, Nur FA, Al-Mandhari AS, El Rabbat M, Hafeez A, Abubakar A. Decisive leadership is a necessity in the COVID-19 response. Lancet, **2020**; 396(10247):295-298.
41. Scheufele DA, Hoffman AJ, Neeley L, Reid CM. Misinformation about science in the public sphere. PNAS, **2021**; 118(15):e2104068118.
42. Walker E, Hernandez AV, Kattan MW. Meta-analysis: its strengths and limitations. Clev Clin J Med. **2008**; 75(6):431-439.
43. Guzzo CA, Furtek CI, Porras AG et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol **2002**;42(10):1122–1133.

44. Amsden GW, Gregory TB, Michalak CA, Glue P, Knirsch CA. Pharmacokinetics of azithromycin and the combination of ivermectin and albendazole when administered alone and concurrently in healthy volunteers. Am J Trop Med Hyg **2007**;76(6):1153-1157.

45. Banerjee K, Nandy M, Dalai CK, Ahmed SN. The Battle against COVID 19 Pandemic: What we Need to Know Before we "Test Fire" Ivermectin. Drug Res (Stuttg) **2020**;70(8):337-340.

46. Kalil AC. Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. JAMA **2020**;323(19):1897–1898.

Table 1. Study characteristics of included randomized controlled trials

Study, year, reference	Country, sample size	IVM dose and duration	Control group	COVID-19 severity according to WHO classification [19]	Positive SARS-CoV-2 RT-PCR (%)	Hospitalized (%)	Mean (SD) or Median (IQR) Age	Female (%)	CVD or CHD (%)	DM (%)	HTN (%)	Evaluated outcomes	Follow-up time (days)
Chachar 2020[28]	Pakistan, 50	12mg; 12 mg at 12 h, and 12mg at 24 h.	SOC	Mild (100%)	100	0	42 (16)	38	8	40	26	Asymptomatic at day 7	7
Krolewiecki 2020[29]	Argentina, 45	0.6 mg/kg qd for 5 days.	SOC	Mild (87%), moderate (13%)	100	100	41 (12)	44	NR	16	13	Viral load at day 5, IVM plasma level	30
Niaee 2020[30]	Iran, 180	Four doses: from 200 µg/kg single dose to 800 µg/kg across 5 days.	SOC	Mild and moderate (unclear distribution)	71	100	56 (45-67)	50	NR	NR	NR	All-cause mortality, time until remission of symptoms, hospital LOS	5
Podder 2020[31]	Banglades h, 62	200 µg/kg single dose.	SOC	Mild (81%), moderate (19%)	100	NR	39 (12)	29	NR	NR	NR	Time to full recovery, viral clearance	10
Ahmed	Banglades	12 mg	Placeb	Mild (100%)	100	100	42	54	0	0	0	Remission of	14

2021[32]	h, 48	qd for 5 days.	o				(NR)					symptoms, hospital LOS, SAE, oxygen requirement, time to viral clearance	
Beltran 2021[33]	Mexico, 73	12 mg if <80 kg; 18 mg if >80 kg, single dose	Placebo	Moderate (74% with PaO_2/FiO2 ratio 100 to 300)	100	100	53 (17)	38	NR	34	32	All-cause mortality, clinical recovery, hospital LOS, AE, respiratory deterioration	28
Chaccour 2021[34]	Spain, 24	400 µg/kg single dose.	Placebo	Mild (100%)	100	0	26 (19-36)	50	0	0	0	All-cause mortality, AE, PCR at day 7	28
Karamat 2021[35]	Pakistan, 86	12 mg single dose.	SOC	Mild (most of them, unclear %)	100	100	39 (42)	15	5.8	12	14	Time to viral clearance, AE	28
Lopez-Medina 2021[36]	Colombia, 398	300 µg/kg qd for 5 days.	Placebo	Mild (100%)	100	1	37 (29-48)	78	1.7	6	13	All-cause mortality, time to complete resolution, AE, SAE, escalation of care	21
Ravikirti 2021[37]	India, 115	12 mg qd for 2 days.	Placebo	Mild (79%), moderate (21%)	Positive RT-PCR or RAT	100	53 (15)	28	11	36	35	All-cause mortality, admission to ICU, requirement	10

												of MV, viral clearance at day 6	

SD: Standard deviation; IQR: Interquartile range; SOC: Standard of care; qd: once a day; NR: Not reported; CVD: Cardiovascular disease; CHD: Coronary heart disease; DM: Diabetes mellitus; HTN: Hypertension; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RT-PCR: Reverse transcription polymerase chain reaction; RAT: Rapid antigen test; PaO_2/FiO_2: ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage); WHO: World Health Organization; AE: adverse events; SAE: severe adverse events; LOS: length of stay; MV: mechanical ventilation; ICU: Intensive care unit.

Table 2. Summary of findings table of the effect of ivermectin compared to standard of care or placebo for COVID-19 patients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	**Risk with ivermectin**			
All-cause mortality follow up: range 5 days to 28 days	6 per 100	**2 per 100** (1 to 7)	**RR 0.37** (0.12 to 1.13)	787 (5 RCTs)	⨁◯◯◯ VERY LOW [a,b]
Length of stay follow up: range 5 days to 28 days	The mean length of Stay was **10** days	MD **0.72 days more** (0.86 fewer to 2.29 more)	-	286 (3 RCTs)	⨁◯◯◯ VERY LOW [c,d]
Adverse events follow up: range 5 days to 28 days	76 per 100	**72 per 100** (65 to 81)	**RR 0.95** (0.85 to 1.07)	467 (3 RCTs)	⨁⨁◯◯ LOW [e]
Severe adverse events follow up: range 5 days to 28 days	0 per 100	**0 per 100** (0 to 0)	**RR 1.39** (0.36 to 5.30)	179 (3 RCTs)	⨁⨁◯◯ LOW [f]
Viral clearance follow up: range 5 days to 28 days	410 per 1,000	**394 per 1,000** (312 to 472)	**RR 0.96** (0.76 to 1.15)	262 (4 RCTs)	⨁⨁◯◯ LOW [g]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; MD: Mean difference
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. RoB: Lopez-Medina et al, Niaee et al and Ravikirti has high risk of bias, Beltran has some concerns and Chaccour haw low risk of bias

b. Imprecision: 95% CI 0.12-1.13

c. RoB: Ahmed et al and Niaee et al have high risk of bias, Beltran has some concerns

d. Imprecision: 95%CI -2.03 to 4.25

e. Krolewiecki et al and Lopez-Medina have high risk of bias, Chaccour have low risk of bias

f. Rob: Ahmed et al, Bukhari et al and Krolewiecki have high risk of bias

g. Rob: Podder et al, Bukhari et al and Ravikiriti has high risk of bias, Chaccour has low risk of bias

Figure Legends

Figure 1. PRISMA flowchart diagram

Figure 2. Effect of ivermectin on all-cause mortality in RCTs of COVID-19 patients.

Figure 3. Effect of ivermectin on length of stay in RCTs of COVID-19 patients.

Figure 4. Effect of ivermectin on adverse events in RCTs of COVID-19 patients.

Figure 5. Effect of ivermectin on severe adverse events in RCTs of COVID-19 patients.

Figure 6. Effect of ivermectin on viral clearance in RCTs of COVID-19 patients.

Figure 1

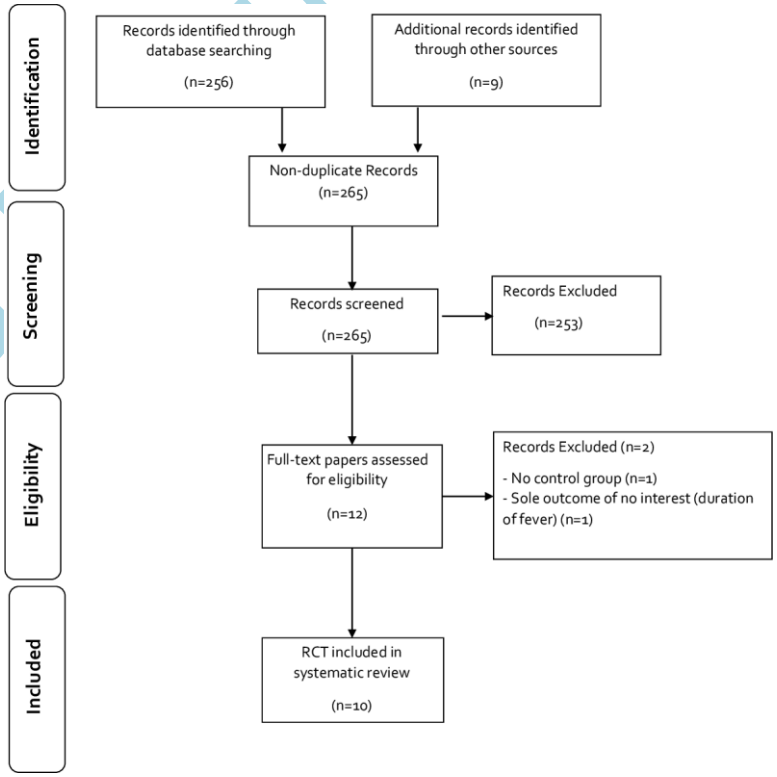

Figure 2

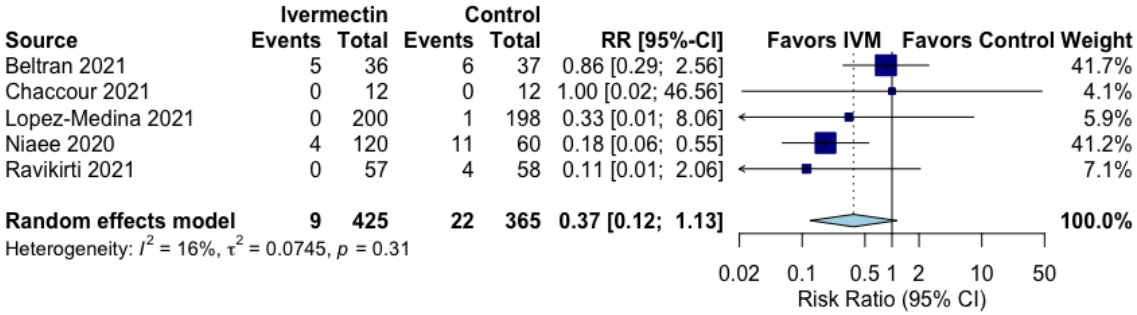

Figure 3

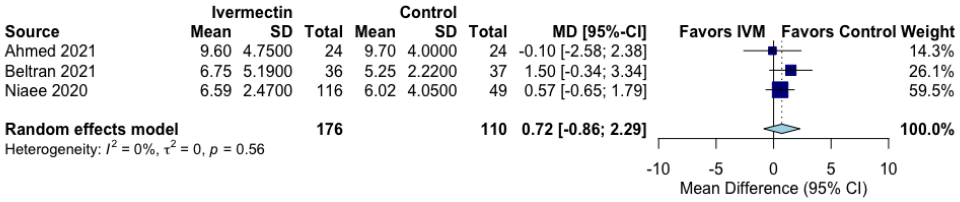

Figure 4

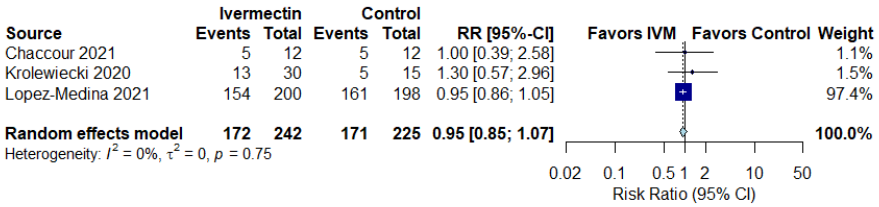

Figure 5

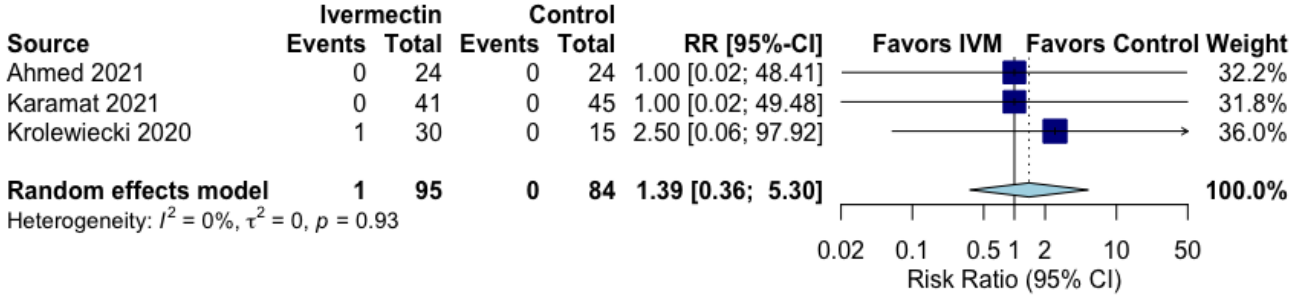

Figure 6