Systematic Review and Meta-analysis of Ivermectin for Treatment of COVID-19: Evidence Beyond the Hype

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Abstract

Background: The role of ivermectin in the treatment of COVID-19 is still under debate, yet the drug has been widely used in some parts of the world, as shown by impressive market data and ivermectin-related adverse event reports. The available body of evidence may have changed over the last months, as studies have been retracted and "standards of care" (SOC) used in control groups have changed with rapidly evolving knowledge on COVID-19 rapidly. This review aims to summarize and critically appraise the evidence of randomized controlled trials (RCTs) of ivermectin, assessing clinical outcomes in COVID-19 patients.

Methods: RCTs evaluating the effects of ivermectin in adult patients with COVID-19 were searched through December 14, 2021, in four databases, L.OVE platform, clinical trial registries and pre-prints platforms. Primary endpoints included all-cause mortality and invasive ventilation requirement. Secondary endpoint was the occurrence of adverse events. Risk of bias was evaluated using the Cochrane Risk of Bias 2.0 tool. Random-effects were used to pool the risk ratios (RRs) of individual trials. The quality of evidence was evaluated using GRADE. Subgroup and sensitivity analysis were performed. The protocol was register in PROSPERO (CRD42021257471)

Results: Twenty-one RCTs fulfilled inclusion criteria (n=2592). Of those, 12 compared ivermectin with placebo and in seven ivermectin associated with SOC was compared to SOC. Most RCTs had some concerns or high risk of bias, mostly due to lack of concealment of the randomization sequence and allocation, lack of blinding and high number of missing cases. Ivermectin did not show an effect in reducing mortality (RR=0.76; 95%CI:0.44 to 1.32) or mechanical ventilation (RR=0.83; 95%CI:0.31 to 2.22) in COVID-19 patients. This effect was consistent when comparing ivermectin vs. placebo, and ivermectin associated with SOC vs. SOC, as well as in sensitivity analysis. Additionally, there was very low quality of evidence regarding adverse effects (RR=0.95; 95%CI: 0.86 to 1.04).

Conclusions: The evidence suggests that ivermectin does not reduce mortality risk and the risk of mechanical ventilation requirement. Although we did not observe an increase in the risk of adverse effects, the evidence is very uncertain regarding this endpoint.

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Introduction

Despite the efforts and the relative success of vaccination against the coronavirus disease 2019 (COVID-19) worldwide, it is possible that the pandemic will persist for a long period, due to the ascension of outcoming variants and anti-vaccine movements around the world [1, 2, 3]. In this context, several drugs, alone or in combination with other drugs, vitamins and minerals were studied to verify the possibility of mitigating the effects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or the symptoms of covid-19 [4]. However, until the present date, few pharmacological therapies have been shown to be effective in reducing the number of hospitalizations, mechanical ventilation and death [5, 6].

The anti-parasite drug ivermectin has grabbed a lot of attention as a potential drug to treat COVID-19, and has become widely used off label, especially in Latin America, to control COVID-19 [7, 8]. The drug has been used for decades to treat parasitic infections, and it is on the list of essential drugs from the World Health Organization (WHO), being considered safe and effective once it is administered in appropriate doses. Several in vitro studies have shown an antiviral effect of ivermectin for flaviviruses, such as Dengue, yellow fever, Zika virus and SARS-CoV-2 as well [9, 10, 11]. In cells infected by SARS-CoV-2, ivermectin has been shown to inhibit the attachment of the virus's spike protein to the human cell membrane, which was able to reduce the viral RNA concentration by almost 5000 fold, what increased hopes for clinical benefit in prevention and treatment of COVID-19 [12, 13, 14]. Nonetheless, for the antiviral effect observed in cell culture to be effective in humans, the dose of ivermectin required would be 17 times higher than the maximum safe dosage allowed per day for patients [12].

The enthusiasm brought by the mechanistic effect has also been questioned in a recent network meta-analysis on the effects of ivermectin on viral clearance. When authors analyzed the data using a fixed effects model approach, there was a significant effect of ivermectin on reducing viral clearance (OR 2.32, 95% equal-tailed credible intervals [CrIs] 1.38 - 3.94); this effect was nonsignificant when they used a random effects model approach (OR 2.70, 95% CrI [1.24, 6.12]), [15] demonstrating how choosing or not the proper methods for analysis can influence the results.

Multiple clinical trials were carried out to assess clinical outcomes [16, 17, 18, 19], with conflicting evidence, and some of these studies were withdrawn given concerns about serious data inconsistencies and research fraud [20, 21, 22, 23] Yet, the drug has been widely used, and has even been called a "COVID-19 miracle drug", supported by vaccine opponents, or even by health authorities in some countries [24]. However, there have been reports from different countries of people being hospitalized after self-medicating and developing serious adverse effects due to ivermectin [25]. The need for evidence synthesis is imperative for medical doctors and the community. Systematic reviews have been published on the topic, but in the majority of them a retracted trial represented more than 10% of the overall effect, [20, 21, 26, 27] which overestimated the benefits. One of those was recently reassessed after the exclusion of this trial, which changed the results from reducing mortality to lack of benefit in this outcome [17]. In another systematic review restricted to studies comparing the drug to placebo or standard care, the authors concluded they were uncertain about the efficacy and safety of ivermectin [28].

As the current evidence on the benefits of ivermectin to treat people with COVID-19 is still debatable and there is a risk of serious adverse events, the WHO living guideline recommends that the drug should only be used within clinical trials, and the IDSA's guideline suggests not using it [4, 29]. Therefore, there is still a gap of reliable and updated evidence synthesis of the effect of ivermectin in COVID-19 patients. This study aims to summarize and critically appraise the evidence of randomized controlled trials (RCTs) of ivermectin, assessing clinical outcomes in inpatients or outpatients with COVID-19.

Methods

This systematic review and meta-analysis was based on recommendations from the Cochrane Guidelines for Systematic Reviews of Interventions and was written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [30, 31]. The review protocol was registered at the PROSPERO (CRD42021257471).

Search strategy

In order to identify randomized clinical trials assessing the effects of ivermectin use in COVID-19 patients, we searched four independent databases to perform the sensitive literature search: MEDLINE, EMBASE; Central (by Cochrane Library) and Latin American and Caribbean Health Science Information (LILACS). We also searched, on an ongoing basis, the Epistemonikos COVID-19 L-OVE platform (Living Overview of the Evidence), which provides an electronic search in 41 databases, trial registries, preprint servers and other sources (**Supplementary material**). In the L-OVE platform, we conducted the search by PICO question (patient/population, intervention, comparison/control, outcome). Additionally, we searched for ongoing registered clinical trials at the National Institute of Health United States National Library of Medicine and pre-prints (medRxiv; bioRxiv), and reference lists of included studies and systematic reviews.

There was no language, date, document type, publication status or geographic restriction for inclusion of records. The last search was conducted on December 14, 2021. Descriptors were identified in Medical Subject Headings (MeSH), *Descritores em Ciências da Saúde* (Decs) and Embase Subject Headings (Emtree). The search strategy was adapted based on descriptors in each database and are presented in the Supplementary material.

Outcomes

The primary outcomes were all-cause mortality and invasive ventilation requirement. Secondary outcome was the percentage of patients who presented adverse events at follow-up.

Eligibility criteria

We included randomized controlled trials that evaluated patients with confirmed COVID-19, or those with suspicion of COVID-19 by clinical symptoms and imaging findings, which compared systemic ivermectin with placebo, no treatment, standard care (as defined by the researchers in the individual studies) or other drugs for COVID-19 treatment, irrespective of disease severity, and assessed any primary or secondary outcomes. Co-interventions had to be the same in both study arms. For the assessment of mortality, we included studies which assessed the patients until recovery or death.

Randomized clinical trials which assessed the use of ivermectin in combination with other drugs when compared to placebo were excluded, as we would not be able to assess the effect of ivermectin itself, as well as those which assessed ivermectin for COVID-19 prevention. Studies in which inhaled ivermectin was used as intervention were also excluded.

Study selection and data extraction

Electronic search results from defined databases were uploaded to the Rayyan Qatar Computing Research Institute [32].

Study selection and data extraction was independently performed by two investigators. A third reviewer resolved any disagreements. For duplicate registrations, only the most recent one was included. Authors initially screened titles and abstracts. Subsequently, they assessed each study to determine whether it met inclusion criteria.

We extracted data on study design (methods, location, setting, inclusion/exclusion criteria, duration and number of participants in each group), participant characteristics (disease severity, age and sex), intervention and comparator characteristics (dose and frequency of ivermectin/comparator, type of comparator, outcome measures at baseline, at the end of follow-up and/or changes in outcome measures from baseline to the end of follow-up).

Quality assessment

Two investigators independently assessed the risk of bias in the selected studies according to the Cochrane Collaboration's tool for assessing risk of bias (RoB 2) [33]. Possible sources of bias in randomized trials include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Three scores of yes, no, and unclear were given to each before mentioned item, referring to high risk, low risk, and unknown risk, respectively. We entered and organized our RoB 2 assessments on an Excel spreadsheet (Microsoft Excel RoB2 Macro) [34]. Reviewers resolved discrepancies by discussion.

The overall certainty of the body of evidence was rated by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, taking into account overall risk of bias, consistency of effect, imprecision, indirectness and publication bias to assess the certainty of the body of evidence [35, 36]. If there were serious concerns in any of these domains, we rated down the quality of evidence. We incorporated the overall RoB2 judgment into our GRADE assessment.

Statistical analysis

Treatment effects were expressed as risk ratios (RRs), as all outcomes were binary. Pooled RR were calculated using random effects models with the Dersimonian and Laird estimator and the Mantel-Haenszel method, as clinical heterogeneity was expected. Statistical heterogeneity among studies effects were investigated by using Cochran Q test and I² statistic. Prediction intervals were not used due to the small number of studies in each meta-analysis.

For the main analysis, we opted to summarize the evidence using subgroups: ivermectin vs placebo and ivermectin associated with SOC vs SOC. Different arms of ivermectin were combined in single arms and, in studies with more than two comparator arms, only placebo or SOC was used as the control in the pooled analysis. The trials in which ivermectin was compared to an active drug were presented only in qualitative analysis. As there is evidence of harm with

hydroxychloroquine and chloroquine [37, 38], it would not be proper to analyze the comparison of ivermectin and hydroxychloroquine or chloroquine. The second analysis compared ivermectin (associated or not with SOC) to no ivermectin (placebo or SOC).

Sensitivity analyses were pre-specified and performed only for the primary outcomes. The effect size was examined by omitting studies individually, excluding simultaneously studies with extreme results, and also taking into account the risk of bias and the percentage of confirmed individuals of the included studies.

A funnel plot was constructed to assess the possibility of publication bias only for the second analysis due to a small number of studies. The symmetry of the plot was evaluated both visually and formally with Egger's test. The implications for our results were assessed by the trim-and-fill method. [39, 40].

Analyses were performed in the Rstudio software, version 4.1.0 (R: A Language and Environment for Statistical Computing, Vienna, Austria), by using the 'Meta' packages, versions 5.0-0.

Data availability

The full dataset and statistical codes will be available on reasonable request from any qualified investigator.

Results

Search results

Our search retrieved 366 studies and 14 registers in progress through four selected database searches, the L.OVE platform. After excluding 51 duplicates, 329 titles and abstracts were screened. Full-text articles for the remaining 26 records were retrieved, of which two were excluded for testing the drug for COVID-19 prophylaxis; [41, 42] two for retraction [21, 23], one was excluded due to the study design (not RCT) [43] and one for a too short follow-up, having not assessed patients until recovery or death [44] (Figure 1). One study was found through hand searching reference lists. Therefore, 21 studies were eligible for inclusion in this systematic review. No additional articles were retrieved from the reference lists of the included studies. Of the 21 included studies, 04 were available as preprints upon the time of submission of the present study [45–48].

Study and patients' characteristics

The main characteristics of the included studies are summarized in Table 1. From the 21 studies, 17 presented the registry number, with 11 international and 6 local registries. In nine of them, the registration was done after the beginning of recruitment, in one of them the recruitment period was not mentioned, and the protocols of three studies could not be retrieved for the registration date to be checked. In eight studies, there were amends in the protocol after the registration [19, 45, 47, 48, 49, 50, 51, 52].

Table 1
Main characteristics of included studies

Reference	Trial registration number	Setting/Location and number of centers	Recruitment period	COVID-19 diagnosis method and % confirmed	Disease severity	Other inclusion criteria	Exclusion criteria
Ivermectin vs. placebo							
Ahmed et al. (2021) [16]	NA	Hospital at Dhaka (Bangladesh) 1 center	Not clear	RT-PCR 100%	Not clear	Admitted to the hospital within the last 7 days; presence of fever (>37,5°C), cough and/or sore throat	Allergy to doxycycline, potential ivermectin chronicity, ivermectin last 7 day breastfeeding in other R month.
Babalola et al. (2021) [74]	NA	Lagos University Teaching Hospital (Nigeria) 1 center	May to November, 2020	RT-PCR 100%	Asymptomatic or mild/moderate symptoms	NA	COVID-19 requiring thrombolysis or unconscious
Biber et al. (2021) [45]	NCT04429711 (June 11 2020)	Hotels in Tel-Aviv at Jerusalem and Ashkelon (Israel) 2 centers	May, 2020 to January, 2021	RT-PCR 100%	Mild to moderate not requiring O ₂ and asymptomatic cases	Not pregnant, up to 7 days of symptoms onset	Weight < 40 kg, the drugs medication, other RCT value > 3, consecutive
Bounfrate et al. (2021) [47]	NCT04438850 (June 18 2020)	Outpatients laboratory-confirmed COVID-19 during the study period (Italy) 4 centers	July, 2020 to May, 2021	RT-PCR 100%	Mild, not requiring hospitalization or O ₂ supplementation	Asymptomatic or oligosymptomatic disease	Pregnancy, dialysis, condition months, antiviral/phosphat treatment
Chaccour et al. (2021) [50]	NCT04390022 (May 15 2020)	University Clinical of Navarra (Spain) 1 center	July to September, 2020	RT-PCR 100%	Non-severe	<72h of cough or fever	Positive IgG, considered severe disease, pneumonia
Chachar et al. (2020) [79]	NCT04739410 (February 4, 2020)	Fatima Memorial Hospital at Lahore (Pakistan) Number not clear	May to June, 2020	RT-PCR 100%	Mild	NA	Known severe disease, to ivermectin breastfeeding symptom cytokine, malignant cirrhosis
Beltran-Gonzalez et al. (2021) [48]	NCT04391127 (May 18, 2020)	Hospital Centerio Miguel Hidalgo in the state of Aguascalientes (Mexico) 1 center	April to June, 2020	Confirmed or suspected % not informed	COVID-19 pneumonia (CO-RADS classification)	Suspected or confirmed COVID-19 cases as well as the pneumonia ATS criteria, hospitalization	Requirement volumes, response therapy of
Krolewiecki et al. (2021) [54]	cTRI Trial Data 2020/08/027225 (August 18, 2020)	Hospitals in the metropolitan area of Buenos Aires (Argentina) 4 centers	May to September, 2020	RT-PCR 100%	Disease stages 3 to 5 from the WHO 8-category ordinal scale of clinical status and no requiring ICU admission	NA	Use of immunosuppressants 30 days, pregnancy, poorly controlled, known ivermectin
López-Medina et al. (2021) [19]	NCT04405843 (May 26, 2020)	Colombian state's health department electronic database(Colombia) 1 center	July to November, 2020	RT-PCR or antigen 100%	Mild	Symptoms began within the previous 7 days	Pregnancy, hospitalization, high-flow, asymptomatic pneumonia, ivermectin 5 days, hypertension, dysfunction, test result, ULN.

Reference	Trial registration number	Setting/Location and number of centers	Recruitment period	COVID-19 diagnosis method and % confirmed	Disease severity	Other inclusion criteria	Exclusion
Mohan et al. (2021) [76]	CTRI Trial Data 2020/06/026001 (June 21, 2020)	COVID-19 facility at the National Cancer Institute, All India Institute of Medical Sciences, New Delhi (India) Number not clear	July to September, 2020	RT-PCR or antigen 79.6%	Non-severe: mild and moderate	NA	Pregnancy, hypertension, CKD with mL/min , transaminase, myocardial failure $\leq$ enrollment, other severe enrollment
Ravikirti et al. (2021) [53]	CTRI Trial Data 2020/08/027225 (August 18, 2020)	COVID-19 hospital (India) 1 center	August to October, 2020	RT-PCR or rapid antigen test 100%	Mild or moderate disease	NA	Severe disease or adverse events, ivermectin intolerance, inability to participate, use of ivermectin course of pregnancy
Vallejos et al. (2021) [18]	NCT04529525 (August 27, 2020)	Province of Corrientes (Argentina) Number not clear	August 19th 2020 - February 22nd 2021	RT-PCR 100%	Not informed	Individuals $\geq$ 18 years, residing in the province of Corrientes. If they are women of childbearing age, they should be using a contraceptive method of proven efficacy and safety. All individuals were to weigh at the time of inclusion $\geq$ 48 kg.	Home O_2 hospitalization at the time of inclusion, history of COVID-19, breastfeeding, to ivermectin, component placebo, treatment, concomitant disease, severe liver disease, expected to participate in study, administration days
Ivermectin + SOC vs. SOC with no placebo							
Abd-Elsalam et al. (2021) [49]	NCT04403555 (May 23 2020)	Tanta and Assiut University Hospitals (Egypt) 2 centers	March to October, 2020	RT-PCR 100%	Mild to moderate	NA	Allergy or the drugs pregnant mothers, cardiac problems
Bukhari et al. (2021) [46]	NCT04392713 (May 17 2020)	Combined Military Hospital Lahore (Pakistan) 1 center	March to June, 2020	RT-PCR 100%	Either asymptomatic or mild/moderate symptoms	NA	Severe symptoms, cytokine storm, with uncontrolled comorbidities, immunocompromised, taking CY inducers, oxygen re to $\text{FiO}_2 \geq$
Faisal et al. (2020) [76]	NA	Shah Care Hospital (Pakistan) 1 center	April to May, 2020	RT-PCR 100%	Not informed	NA	Severe comorbidities, diabetes, cardiovascular disease, and $\text{O}_2 \text{ de}$
Okumuş et al. (2021) [51]	NCT04646109 (November 27, 2020)	Research and Education Hospital (Turkey) 4 centers	May to September, 2020	RT-PCR 100%	Severe pneumonia	NA	Children < 18 years, pregnant, breastfeeding, autoimmune liver or CKD, immunosuppression, mutation gene and mutation
Podder et al. (2020) [67]	NA	Debidwar Upazila (sub-district) Health Complex (Bangladesh) 1 center	May to July, 2020	RT-PCR 100%	Mild to moderate	NA	Known prior hypertension, pregnancy, patients taking antimicrobials, hydroxychloroquine > 7 days

Reference	Trial registration number	Setting/Location and number of centers	Recruitment period	COVID-19 diagnosis method and % confirmed	Disease severity	Other inclusion criteria	Exclusion
Pott-Junior et al. (2021) [52]	NCT04431466 (June 11,2020)	Academic Hospital of Federal University of São Carlos(Brazil) 1 center	NA	RT-PCR 100%	Mild	Eastern Cooperative Oncology Group score 0-1	Patients r ingest/at clinical ol would ha risk to pa any abno that requi evaluatio hypersen compone breastfee <15kg, Gf 30mL/mi fold ULN.
Shahbaznejad et al. (2021) [77]	Iraan Registry 20111224008507N3 (date not available)	Hospitals of University of Medical Sciences(Iran) 2 centers	May to July, 2020	RT-PCR or symptoms+contact or chest CT 64%	Moderate to severe	NA	History of kidney di treatment angiotens inhibitor c receptor z immunoc or breastf
Ivermectin vs. active comparator							
Galan et al. (2021) [78]	Brazilian Clinical Trial Database 8h7q82 (August 28, 2020)	General Hospital of Roraima (Brazil) 1 center	May to July, 2020	RT-PCR or IgM 100%	Severe form of disease: dyspnea, tachypnea, peripheral oxygen saturation < 93%, PaO ₂ /FiO ₂ ratio <300 or pulmonary infiltrate > 50%.	Hospitalized by COVID-19	Patients c indigenou fluent in p understai methods ill patient accompa represent reject par patients v arrhythm prolonga and previ medicatio than 24 h
Niaee et al. (2020) [63]	Iraan Registry of Clinical Trials 20200408046987N1 (date not available)	Public hospitals in Qazvin and Khuzestan(Iran) 5 centers	June to July, 2020	RT-PCR or symptoms+contact or chest CT 71%	Mild to moderate	NA	Children, immunos women, k reaction t drugs, ch malignan patients z the patier and/or ur and/or fo

Table 1
b. Main characteristics of included studies (continued)

Reference	Randomized sample	Final sample	Age*	Ivermectin	Comparator	Funding
Ivermectin vs. placebo						
Ahmed et al. (2021) [16]	72	68	42	A1: Ivermectin 12 mg for 5 days; A2: Ivermectin 12 mg for 4 days	Placebo	Beximco Pharmaceutical Limited, Bangladesh.
Babalola et al. (2021) [74]	63	62	44.1 ± 14.7	A1: Ivermectin 6mg (given every 84 h) twice a week; A2: Ivermectin 12mg (given every 84 h) for 2 weeks + SOC ²	SOC ² + placebo	Not reported
Biber et al. (2021) [45]	116	89	35 (28-47)	Ivermectin 0.2 mg/kg for 3 days	Placebo	Not reported
Bounfrate et al. (2021) [47]	93	93	47 years (31.0-58.0)	Single dose 54 ivermectin 600 µg/kg plus placebo for 5 days (arm B); single dose ivermectin 1200 µg/kg for 5 days (arm C).	Placebo	Italian Ministry of Health
Chaccour et al. (2021) [50]	24	24	NI	Ivermectin 0.4 mg/kg (single oral)	Placebo	ISGlobal, Barcelona Institute for Global Health and Clínica Universidad de Navarra
Chachar et al. (2020) [79]	50	50	41.8 ± 15.7	Ivermectin 12 mg (3 tablet in stat, 12 hour and 24 hour)	Placebo	Not reported
Beltran-Gonzalez et al. (2021) [48]	108	106	53.8 ± 16.9	Ivermectin 0.2mg/kg for 4 days	A1: Placebo A2: HCQ***	Not reported
Krolewiecki et al. (2021) [54]	45	45	NI	Ivermectin 0.6 mg/kg/day for 5 consecutive days with either breakfast or lunch at approximately 24 hours intervals	Placebo	IP-COVID-19-625, Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación, Argentina and Laboratorio ELEA/Phoenix, Argentina.
López-Medina et al. (2021) [19]	476	398	37 (29 - 47.7)	Ivermectin 0.3 mg/kg for 5 days	Placebo	Centro de Estudios en Infectología Pediátrica (grant ScDi823).
Mohan et al. (2021) [76]	157	152**	35.3 ± 10.4	A1: Ivermectin 12 mg (single dose); A2: Ivermectin 24 mg (single dose)	Placebo	Science and Engineering Research Board, Department of Science and Technology, Government of India
Ravikirti et al. (2021) [53]	115	112	52.5 ± 14.7	Ivermectin 12 mg (single dose) for 2 days	Placebo	Ivermectin tablets were procured from the learning resource allowance of the principal investigator. Placebo tablets were provided by Sun Pharma Pvt. Ltd.
Vallejos et al. (2021) [18]	501	501	42.49 (± 15.51)	Ivermectin ⁹ + SOC ⁷	Placebo + SOC ⁷	Not reported
Ivermectin + SOC vs. SOC with no placebo						
Abd-El salam et al. (2021) [49]	164	164	NI	Ivermectin 12 mg (single dose) for 3 days + SOC ¹	SOC ³	NI

Reference	Randomized sample	Final sample	Age*	Ivermectin	Comparator	Funding
Bukhari et al. (2021) [46]	100	86	NI	Ivermectin 12 mg (single dose) + SOC ³	SOC ⁴	Not reported
Faisal et al. (2020)	100	100	NI	Ivermectin 12mg once a day for 5 days + azitromycin + SOC ⁴	Azithromycin + SOC ⁵	Not reported
Okumuş et al. (2021) [51]	66	60*	NI	Ivermectin 0.2 mg/kg for 5 days + SOC ⁵	SOC ⁶	Afyonkarahisar Health Science University Scientific Research project
Podder et al. (2020) [67]	82	62	39.2 ± 12.1	Ivermectin 0.2 mg/kg (single dose) + SOC ⁶	SOC ⁷	Self-financiated
Pott-Junior et al. (2021) [52]	32	31	49.4 ± 14.6	A1: Ivermectin 0.1 mg/kg (single dose) + SOC ⁷ ; A2: Ivermectin 0.2 mg/kg (single dose) + SOC ⁷ ; A3: Ivermectin 0.4 mg/kg + (single dose) SOC ⁷	SOC ⁸	Not reported
Shahbaznejad et al. (2021) [77]	70	69	46.4 ± 22.5	Ivermectin 0.2 mg/kg + SOC ⁸	SOC ⁹	Not reported
Ivermectin vs. active comparator						
Galan et al. (2021)[78]	167	167	53.4 ± 15.6	A1: Ivermectin (14 mg once at day 0 + 1 placebo tablet at day 0, and once daily from day 1 to day 2, + 1 placebo tablet daily from day 3 to 4, total dose 42 mg; A2: Ivermectin (14 mg once at day 0 + 1 placebo tablet at day 0, and once daily from day 1 to day 2, + 1 placebo tablet daily from day 3 to 4, total dose 42 mg)	A1: Hydroxychloroquine A2:CQ diphosphate + HCQ sulfate	NI
Niaee et al. (2020) [63]	180	180	56 (45-67)	A1: Ivermectin 0,2mg/kg (1 tablet, single dose); A2:Ivermectin 0,2 mg/kg (3 tablet in day 1, 3 and 5); A3: Ivermectin 0,4 mg/Kg (2 tablets per day, single dose); A4: Ivermectin (0.4 mg/kg, 4 tablets in day 1; 0.2 mg/kg, 4 tablets in day 3; 0.2 mg/kg, 4 tablets in day 5)	HCQ	Research deputy of Qazvin University of Medical Sciences and Science and Technology Park, Qazvin, Iran.
A: arm; CKD: chronic kidney disease; CKD-EPI:Chronic Kidney Disease Epidemiology Collaboration; Cl: clearance; CO-RADS: COVID-19 Reporting and Data System [74]; CNS: central nervous system; GFR: glomerular filtration rate; HCQ: hydroxychloroquine; ICU: intensive care unit; MV: mechanical ventilation; N: no, NA: not applicable, NI: not informed, O ₂ :oxygen; QTc: corrected Qt interval; RCT: randomized controlled trial; SOC: standard of care;Y: yes, ULN: upper limit of normality.						
* Numbers are presented as average ± standard deviation or median (interquartile range)						
* The final sample for adverse effects is different to the final sample for our primary outcomes						
** This arm was not included in the meta-analysis						
¹ Lopinavir/ritonavir.						
² Not informed						
³ Paracetamol, oxygen, fluids (according to the condition of the patient), empiric antibiotic, oseltamivir if needed (75 mg/12 h for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO ₂ less than 60 mm Hg, O ₂ saturation less than 90% despite oxygen or noninvasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock.						
⁴ Oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg SOS.						
⁵ Paracetamol (500mg if needed), Vit C (500mg once a day for 15 days), zinc (20mg twice a day for 15 days) and Vit D (injection PO 200,000units once) supplements.						
⁶ Hydroxychloroquine (2x400mg loading dose followed by 2x200mg, po, 5 days), favipiravir (2x1600mg loading dose followed by 2x600mg maintenance dose, po, total 5 days) and azithromycin (500 mg first day loading dose, followed by 250 mg/day, po, total 5 days)						
⁷ Antipyretics, cough suppressants, and capsule doxycycline 100 mg every 12 hours for seven days.						
⁸ Hydroxychloroquine and/or lopinavir/ritonavir.						
⁹ Those weighing up to 80 Kg received 2 tablets of 6 mg (mg) each at inclusion and another 2 tablets of 6 mg each 24 h after the first dose (total 24 mg). Those weighing more than 80 kg and up to 110 kg received 3 tablets of 6 mg each at inclusion and another 3 tablets of 6 mg each 24 h after the first dose (total 36 mg). Those weighing more than 110 kg received 4 tablets of 6 mg each at inclusion and another 4 tablets of 6 mg each 24 h after the first dose (total 48 mg).						

All studies had parallel designs. Eleven studies took place in Asia (Pakistan n=03; India n=02; Bangladesh n=02; Iran n=02; Turkey n=01; Israel n=01); six were in South America (Argentina n=02; Colombia n=01; Mexico n=01; Brazil n=02); two in Africa (Egypt n=01; Nigeria n=01) and two in Europe (Spain n=01; Italy n=01). The number of centers included in each study ranged from one to five, from hospitals (66.7% n=14) to health centers (14.3% n=03).

Included studies provided a total of 2592 subjects. Sex was reported in 19 studies (n=2137), and of those 62.3% were men. Age was reported in 15 studies, ranging from 35 to 56 years with a mean of 42 years old. Of the 15 studies that reported disease severity at baseline (n=1734), 927 (53.5%) patients were mild; 442 (25.5%) moderate, 281 (16.2%) severe, and 86 (5.0%) patients were reported to be between mild to moderate disease severity.

In 12 studies ivermectin was compared to placebo and in 7 ivermectin was associated with SOC and compared to SOC alone. SOC definition varied considerably among them, possibly including antibiotics, antivirals, hydroxychloroquine, vitamins and mineral supplements (Table 1). Ivermectin doses ranged from 0.4 mg/kg (single oral) to 12 mg (3 tablets 0, 12 and 24 hour), for 7 to 90 days. The average follow-up was 23 days (minimum of 7 days and maximum of 90 days).

From the 21 studies, only 10 reported the funding source, three of them funded by the pharmaceutical industry [16, 53, 54].

Quality assessment

The risk of bias for each study is depicted in Figures S1 and S2. From the eleven studies which assessed mortality when ivermectin was compared to placebo, four had high risk of bias, four had some concerns and three had low risk of bias. When taking into account only studies which reported any events, one had high risk of bias, one had some concerns and two low risk of bias. From the seven studies in which ivermectin + SOC was compared to SOC, five studies had high risk of bias and two had some concerns. When taking into account only the two studies which reported any events, both had some concerns of bias.

From the nine studies which assessed the mechanical ventilation requirement endpoint, in five ivermectin was compared to placebo. One of those had high risk of bias, two some concerns and two low risk of bias. Of the two with events, one had low risk of bias and the other some concerns. When ivermectin associated to SOC was compared to SOC, one study had high risk of bias and two some concerns, all of these had events.

The main limitations of those with high risk were lack of concealment of the randomization sequence and allocation when distributing patients to the study groups, lack of adequate blinding of patients, treating physicians and outcome assessors, in addition to the relevant number of subjects' exclusion after randomization.

Primary outcomes

Table 2 shows the summary of findings (SOF) table with the GRADE classification of the quality of evidence for the primary outcomes.

Table 2
Summary of findings (SOF) table for the primary outcomes

Outcome	Study population	Relative effect RR (95% CI)	Certainty of the evidence (GRADE)
Mortality	2,162 patients (18 studies)	RR 0.76 (0.44-1.32)	⊕⊕ Low
Mechanical ventilation requirement	1,536 (9 studies)	RR 0.96; (0.43-2.18)	⊕⊕ Low
GRADE: Grading of Recommendations Assessment, Development and Evaluation, RR: relative risk			
*The body of evidence was graded as "low" due to serious risk of bias and imprecision.			

Treatment with ivermectin did not show significant effect on mortality (RR=0.76; 95%CI 0.44 to 1.32; $P=0\%$) (Figure 2) or the need for invasive ventilation (RR=0.96; 95%CI: 0.43 to 2.18; $P=0\%$) (Figure 3), with no difference whether ivermectin was compared to placebo or whether ivermectin associated with SOC was compared to SOC ($p=0.93$ for mortality and $p=0.63$ for ventilation). For mortality, the study with the heaviest weight and the one with the second heaviest, both tending to benefit from ivermectin, had high risk and some concerns of bias, respectively.

Visual inspection of the funnel plots (Figure S3), Eggers test ($p=0.47$ for mortality and $p=0.94$ for mechanical ventilation) and "Trim and fill" method for mortality (RR=0.82; 95%CI: 0.48 to 1.41) and for ventilation (RR=0.96; 95%CI: 0.42 to 2.18) showed no evidence of publication bias, even those results comes from small sample size.

Results did not differ substantially in sensitivity analysis taking into account the risk of bias and the percentage of confirmed individuals of the included studies (Figure 4) and by removing each study one-by-one or excluding simultaneously studies with extreme results (Figure S4).

Secondary outcome

Overall, ivermectin does not show evidence of association with the occurrence of adverse effects when compared with control (RR=0.95; 95%CI: 0.86 to 1.04; $P=0\%$) (Figure S6), with no difference between subgroups ($p=0.83$).

Discussion

We conducted a comprehensive search on the impact of ivermectin for the management of patients with COVID-19 and observed that ivermectin does not have an effect in reducing mortality or mechanical ventilation in patients with COVID-19. Despite the low quality of evidence, this effect was consistent when comparing ivermectin vs. placebo, and ivermectin associated with SOC vs. SOC, as well as in sensitivity analysis. Additionally, there was very low quality of evidence of no increase in risk of adverse effects.

Despite not being recommended in current COVID-19 guidelines by WHO and IDSA [4, 29], the prevalence of self-medication during COVID-19 course was high, and ivermectin was one of the medications commonly used, as shown in a recent systematic review [55]. This may be related to self-medication, misinformation in the media, science denialism and low access to health services combined with the low cost of ivermectin, and the belief that it has a safe adverse effect profile [55, 56]. In Brazil, for example, the Ministry of Health included the medication in its COVID-19 guidelines. Up to August 2021, estimates from the Brazilian Parliamentary Commission of Inquiry showed that only one pharmaceutical company sold more than 83 million US dollars in ivermectin [57, 58].

Living systematic reviews may have changed this scenario, as they are supposed to incorporate all new relevant evidence as they become available [59]. Nonetheless, with the overwhelming number of studies published in COVID-19 pandemic area, keeping the living reviews updated is a challenge difficult to overcome. This challenge is even more complex when the living reviews propose to assess different comparisons with multiple drugs and evolving SOC. Ivermectin has been the subject of two systematic reviews. The British Medical Journal's living review was last updated not so recently, in April 2021, and suggested a possible reduction in mortality in patients who used ivermectin, when compared to standard of care (RR 0.31 95% CI 0.14-0.72). The authors highlighted the fact that data was limited by extremely few events, leading to very serious imprecision, and serious risk of bias [27]. The other living review, by the Pan American Organization, has been recently updated in December 2021, and analyzed the evidence from 14 studies. The authors reported that pooled estimates suggested mortality reduction with ivermectin (RR 0.50 95% CI 0.29-0.87), an effect that was no longer apparent when a subgroup analysis of the three studies classified as low risk of bias was performed (RR 0.96 95%CI 0.58 to 1.59) [60]. These two living reviews were not updated after Elgazzar et al study was retracted. We reckon that another update must also take into account the fact that studies that compared ivermectin with hydroxychloroquine may now be clinically inappropriate, and therefore should not be kept in the pooled analysis studies, as evidence of harm with the use of hydroxychloroquine is now robust [37].

Differently from our results, a recent review has found substantial differences in the results of studies with or without important methodological limitations, highlighting that important benefits associated with ivermectin were based on potentially biased results [61]. Because this review was mainly interested in investigating "bias as a source of inconsistency", as stated in the review title, the authors included in the pooled analysis the aforementioned retracted trial, as well as studies in which ivermectin was compared to other drugs, such as hydroxychloroquine [62, 63]. This approach resulted in pooling data from 5592 patients, more than twice the number of patients included in our review. We strongly believe the best body of evidence now available should not include such studies.

In the present study, the certainty of the evidence on mortality and need for mechanical ventilation was ranked as low (GRADE) due serious concerns about risk of bias and imprecision. Methodological limitations were mainly due to lack of adequate blinding of patients and outcome assessors and high number of losses after randomization. Additional concerns included the fact that some studies were not pre-registered prior to enrolling patients, others had the protocol modified, and the majority did not report the funding source, although three of them were sponsored by pharmaceutical companies. However, as mortality and mechanical ventilation are hard endpoints, and our findings were negative, those sources of bias might not have had a great impact on these outcomes. Instead, it could have been influential for assessing adverse effects. In fact, studies usually assess overall adverse effects, without separating them according to severity, and this is a limitation addressing this outcome. For example, in Okumus et al, while patients who took ivermectin had serious neurological adverse effects which require drug discontinuation, the control group had only nausea, vomiting or two-fold increase in alanine transaminase. None of these side effects were severe enough to require termination of treatment in the control group [51].

Another limitation is the low event rate. Among the 20 studies that could be assessed for mortality, 12 did not have any events. COVID-19 severity varied among the different studies, but the majority of them included patients with mild to moderate disease. Therefore, mortality is expected to be very low in this context. The same applies for mechanical ventilation requirement.

One strength of the present review is to have applied strict methodological criteria, to have performed a broad search in several databases, and to be comprehensive, analyzing not only studies comparing the drug to placebo, but also those in which ivermectin associated with SOC was compared to SOC, in a stratified analysis. This is different from a recent Cochrane review, with the last search performed in May 2021, which selected only placebo-controlled studies. Only two studies were included in the pooled analysis to assess mortality and mechanical ventilation requirement [28]. As aforementioned, a recent network meta-analysis has shown how different statistical approaches (random vs. fixed) lead to different results on the effects of ivermectin on viral clearance [15]. This shows how misleading results may be when inappropriate methods are used. Random effects model is more appropriate in this context, as studies included patients with heterogeneous disease severity and the management was different among the different studies. This could be observed by the several definitions of standard of care. As we should not assume a common effect size to all studies included, and the goal of the analysis is to generalize to a range of scenarios, a random effect approach is recommended [64].

The urgent demand for treatment options for COVID-19 has created the need for randomized clinical trials. Scientists tested several approved drugs against the disease, "throwing every already-approved drug" [8], and the rush to conduct those trials led to conduct and publication of studies with varied quality and

important methodological limitations. This "provided fertile ground for even poorly evidenced claims of efficacy to be amplified, both in the scientific literature and on social media" [20]. This is very problematic, as results from studies with high risk of bias were quickly widespread in clinical practice and public policy and SOC were also adopted in a rush in different countries. Even worse, different governments were reluctant to change their protocols after the evidence had shown that some drugs should not be used. In Brazil, for example, a huge polarization and politicization disseminated the SOC supported by the Brazilian President, known as "kit COVID-19" which included hydroxychloroquine, ivermectin and azithromycin [65]. Consequently, studies have included varied and clinically inappropriate options as they defined their comparators as SOC.

For example, months after evidence that hydroxychloroquine may increase the risk of death was available [66] a research protocol of Beltran-Gonzalez et al study was registered, in Brazil [48]. With regard to antibiotics as SOC in patients with COVID without evidence of bacterial pneumonia (for example doxycycline or azithromycin), the World Health Organization advised against the practice in May 2020; still, two studies which started recruitment at that month kept antibiotics in their definition of SOC [51, 67].

There are ethical considerations in this regard, exposing patients to harm and, in the case of antibiotics, contributing to the emergence of antibiotic resistance [68], which is a major issue worldwide. In a letter to the editor about Podder et al, Meneses pointed out important ethical issues. He observed that the authors mentioned approval of their study by the director of the health center, but apparently there was methodological and ethical evaluation by an institutional board [69].

Niaee et al, which included hydroxychloroquine in the comparison arms and was the main study which has shown benefits of ivermectin in clinical outcomes after the aforementioned retractions, has been recently questioned [64]. An editorial note was published in October 2021, reporting concerns about various aspects of the study, including possible problems in the randomization of participants [65]. This raises concerns that flawed evidence in studies with ivermectin or other drugs may impact in systematic reviews.

Our meta-analysis was innovative for using the Living Overview of Evidence database (L.OVE, issued by Epistemonikis) for a comprehensive search, in addition to the traditional search. L.OVE is a digital tool that compiles articles from several databases, including preprint databases, kept up to date through computational algorithms [70]. A previous analysis has shown that it may be more efficient than the traditional search [71]. Consequently, in terms of databases, our search was broader than other systematic reviews on the topic, and the tool made it easier to update the search regularly. Furthermore, we tried to minimize potential biases in the review process by following the methods recommended by the Cochrane Collaboration [30] and set out in our published PROSPERO protocol [31], which provides transparency in the review process. Additionally, we presented a summary of findings table with GRADE results and assessment, in accordance with the new standards required by Cochrane.

In a recent publication, the authors reflect that besides the retracted studies, several other studies which claim a benefit for ivermectin may be similarly fraught. They highlighted unexplainable mismatches between trial registry updates and published patient demographics and timelines that are not consistent with the veracity of the data collection [20]. Therefore, it is of utmost importance for authors of systematic reviews, before following strict methodological criteria, to keep updated with possible new study retractions. Our sensitivity analysis did not show any difference in the point estimates when individual studies were removed, so we do not expect large changes in point estimates.

Thousands of supporters, many of them anti-vaccine activists, have continued to vigorously campaign for ivermectin use, claiming that the real evidence is being ignored. In the context of misinformation infodemics, some sites have published systematic reviews with meta-analysis on the effectiveness of the use of ivermectin in COVID-19 outcomes (<https://ivmmeta.com> and Home - FLCCC | Front Line COVID-19 Critical Care Alliance (covid19criticalcare.com)). Most reviews have not undergone peer review, do not show the criteria used in the selection of RCT's, do not present records and statistical criteria for evaluating the effect and heterogeneity between studies. According to Roman et al (2021), these sites contribute to misinformation of patients, their families, the general population and health professionals who cannot critically analyze scientific studies.

We believe this transparent and thorough summary may contribute to disseminate truthful evidence. Despite the limitation in the analysis of adverse effects, previous studies list some serious adverse effects, such as toxidermias, encephalopathies, confusional disorders [72]. Associated with the lack of clinical benefit, this should be considered when managing patients with COVID-19.

In conclusion, the evidence suggests that ivermectin does not reduce mortality risk and the risk of mechanical ventilation requirement. Although we did not observe an increase in the risk of adverse effects, the evidence is very uncertain regarding this endpoint.

Abbreviations

COVID-19: coronavirus disease 2019

Decs: Descritores em Ciências da Saúde

IDSA: Infectious Disease Society of America

LILACS: Latin American and Caribbean Health Science Information

L.OVE: Living Overview of the Evidence

MeSH: Medical Subject Headings

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RRs: risk ratios

RCT: randomized controlled trials

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SOC: standard of care

WHO: World Health Organization

Declarations

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

Not applicable, as this is a systematic review.

Data availability statement

Data is available upon reasonable request.

Data access, responsibility, and analysis

The lead authors MSM and PKZ had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration

The lead authors MSM and PKZ affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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The sponsors had no role in study design; data collection, management, analysis, and interpretation; writing the manuscript; and deciding to submit it for publication. MSM and MCP had full access to all the data in the study and had responsibility for the decision to submit for publication.

Author contribution

Substantial contributions to the conception or design of the work: MSM and NSG

Substantial contributions to the acquisition, analysis, or interpretation of data for the work: MSM, NSG, KCM, VSC, LCS, SK, RAV, GR, PKZ.

Revised the manuscript critically for important intellectual content: all authors

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Figures

Figure 1
Flow of information through the different phases of the systematic review. The flowchart was adapted from the Preferred Reporting Items for Systematic Review and Meta-Analyses flow chart model.

Figure 2
Forest plots showing the risk of mortality in patients who took ivermectin compared to controls, stratified by placebo or other drugs. RR: relative risk.

* This study had two control groups, one with placebo and the other with another drug. We included in the pooled analysis only the comparator arm which used placebo.

Figure 3
Forest plots showing the risk of mechanical ventilation requirement in patients who took ivermectin compared to controls, stratified by placebo or other drugs.
RR: relative risk.

Figure 4
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Forest plots showing sensitivity analysis of mortality and mechanical ventilation according to the percentage of confirmed COVID-19 patients and risk of bias.
RR: relative risk.

Supplementary Files

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