Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

Ivermectin and mortality in patients with COVID-19: A systematic review, meta-analysis, and meta-regression of randomized controlled trials

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ABSTRACT

Aims: This systematic review and meta-analysis aims to investigate the effect of ivermectin on mortality in patients with COVID-19.
Methods: A comprehensive systematic literature search was performed using PubMed, Scopus, Embase, and Clinicaltrials.gov from the inception of databases up until April 9, 2021. The intervention group was ivermectin and the control group was standard of care or placebo. The primary outcome was mortality reported as risk ratio (RR).
Results: There were 9 RCTs comprising of 1788 patients included in this meta-analysis. Ivermectin was associated with decreased mortality (RR 0.39 [95% 0.20–0.74], p = 0.004; I^2: 58.2%, p = 0.051). Subgroup analysis in patients with severe COVID-19 showed borderline statistical significance towards mortality reduction (RR 0.42 [95% 0.18–1.00], p = 0.052; I^2: 68.3, p = 0.013). The benefit of ivermectin and mortality was reduced by hypertension (RR 1.08 [95% CI 1.03–1.13], p = 0.001); but was not influenced by age (p = 0.657), sex (p = 0.466), diabetes (p = 0.429). Sensitivity analysis using fixed-effect model showed that ivermectin decreased mortality in general (RR 0.43 [95% CI 0.29–0.62], p < 0.001) and severe COVID-19 subgroup (RR 0.48 [95% CI 0.32–0.72], p < 0.001).
Conclusions: Ivermectin was associated with decreased mortality in COVID-19 with a low certainty of evidence. Further adequately powered double-blinded placebo-controlled RCTs are required for definite conclusion.

1. Protocol registration

PROSPERO: CRD42021247986.

2. Background

Coronavirus disease 2019 (COVID-19) is still one of the most prevalent diseases despite the best effort to contain them [1]. Although most of the patients only have mild-moderate clinical symptoms, a significant proportion of them developed acute complications that may be lethal [2–4]. Lethal complications are usually linked with inflammation associated with COVID-19, in which there is elevation of tumor necrosis factor (TNF) -α, C-reactive protein (CRP), D-dimer, interferon (IF) -γ and interleukin (IL) [5,6]. Most medications that is touted for COVID-19 failed to demonstrate benefit in randomized controlled trials (RCTs). In an effort to find treatment, there is a mounting interest on repurposing the available antiviral and antiparasitic medications to treat COVID-19.

One of the most promising drugs is ivermectin, a macrocyclic lactone antiparasitic drug, well known for its broad spectrum antiparasitic activity, and has excellent safety profile [7,8]. Highly

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versatile, ivermectin shows activity beyond its antiparasitic properties, including antimicrobial, antiviral, and anticancer [9–14]. Recent studies have shown its antiviral activity against several RNA viruses, therefore raising the possibility to be used as an alternative agent against SARS-CoV2 [15–18]. This systematic review and meta-analysis aims to investigate the effect of ivermectin on mortality in patients with COVID-19 by pooling randomized controlled trials (RCTs) that were designed to evaluate ivermectin versus standard of care or placebo.

3. Materials and methods

This is a Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) compliant systematic review and meta-analysis, registered in PROSPERO (CRD42021247986).

3.1. Search strategy and study selection

A comprehensive systematic literature search was performed using PubMed, Scopus, Embase, and Clinicaltrials.gov (Filter: Completed) using terms "(SARS-CoV-2 OR COVID-19 OR 2019-nCoV OR Coronavirus Disease 2019) AND (ivermectin)" from the inception of databases up until April 9, 2021. Two independent authors screened through the title/abstracts and potentially eligible articles were assessed based on the inclusion and exclusion criteria. Discrepancies during this process were resolved by discussion.

3.2. Inclusion and exclusion criteria

Studies that met all of the following criteria were included: 1) randomized controlled trials (RCTs) comparing ivermectin versus control in patients with COVID-19 and 2) mortality.

Studies that met one of the following criteria were excluded: 1) conference papers/abstracts-only publication, 2) non-research letters, 3) reviews, and 4) editorial/commentaries. We did not impose language restrictions.

3.3. Data extraction

Data extraction was performed by two independent authors. The data of interest for this systematic review were the first author, study design, ivermectin dose, sample size, percentage of severe COVID-19, age, sex, diabetes, hypertension, coronary artery disease, and mortality. Discrepancies were resolved by discussion.

3.4. Risk of Bias Assessment

To assess the risk of bias, two independent authors used the Cochrane Risk of Bias (RoB) Assessment for RCTs. Discrepancies were resolved by discussion. Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to determine the certainty of evidence.

3.5. Intervention and outcome

The intervention group was ivermectin with or without standard of care. The control group was placebo or standard of care defined by each trial. The primary outcome was mortality, defined as clinically validated non-survivor/death. The pooled effect estimate was reported as risk ratio (RR).

3.6. Statistical analysis

To calculate the pooled RRs for the primary outcome, we performed Der-Simonian Laird random-effects meta-analysis, regardless of heterogeneity. The p-values in this study was two-tailed and a value of ≤ 0.05 were considered as statistically significant. Cochran's Q test and I^2 statistics were used to evaluate heterogeneity, I^2 values above 50% or/and p-value below 0.10 indicates significant heterogeneity. Funnel-plot analysis and Egger's test were used to assess publication bias and potential for small-study effects. STATA version 16.0 was used to perform the statistical analysis. Meta-regression analysis was performed for the association between ivermectin and mortality reduction using patients' characteristics as covariates. Sensitivity analysis using Mantel-Haenzsel fixed-effect model was performed.

4. Results

4.1. Baseline characteristics

There were 9 RCTs comprising of 1788 patients included in this systematic review and meta-analysis [Fig. 1] [19–28]. Baseline characteristics of the included studies can be seen in Table 1.

4.2. Ivermectin and mortality

Ivermectin was associated with decreased mortality (RR 0.39 [95% 0.20–0.74], $p = 0.004$; I^2: 58.2%, $p = 0.051$) [Fig. 2]. Subgroup analysis in patients with severe COVID-19 showed borderline statistical significance towards mortality reduction (RR 0.42 [95% 0.18–1.01], $p = 0.052$; I^2: 68.3, $p = 0.013$) [Fig. 3].

4.3. Meta-regression

The benefit of ivermectin and mortality was reduced by hypertension (RR 1.08 [95% CI 1.03–1.13], $p = 0.001$); but was not influenced by age ($p = 0.657$), sex (reference: male, $p = 0.466$), diabetes ($p = 0.429$).

4.4. Risk of Bias Assessment

Risk of bias assessment using Cochrane RoB Tool can be seen in [Fig. 4]. Most of the studies were preprints which may increase bias. Funnel-plot was asymmetrical [Fig. 5] and there is an indication of small-study effects ($p = 0.005$).

4.5. Certainty of evidence

GRADE Assessment indicates that the mortality lowering effect of ivermectin has a low certainty of evidence, with an absolute risk reduction of 53 fewer per 1000 (from 71 fewer to 21 fewer) (Table 2).

4.6. Sensitivity analysis

Sensitivity analysis using fixed-effect model showed that ivermectin was significantly associated with decreased mortality in general (RR 0.43 [95% CI 0.29–0.62], $p < 0.001$) and severe COVID-19 subgroup (RR 0.48 [95% CI 0.32–0.72], $p < 0.001$).

5. Discussion

This meta-analysis showed that ivermectin reduce mortality in patients with COVID-19 with a low certainty of evidence. Meta-regression indicates that the benefit of ivermectin use was smaller in patients with hypertension.

Hypertension is associated with worse prognosis in patients with COVID-19, and drugs such as angiotensin receptor blockers might affect their prognosis [29,30]. The included studies did not

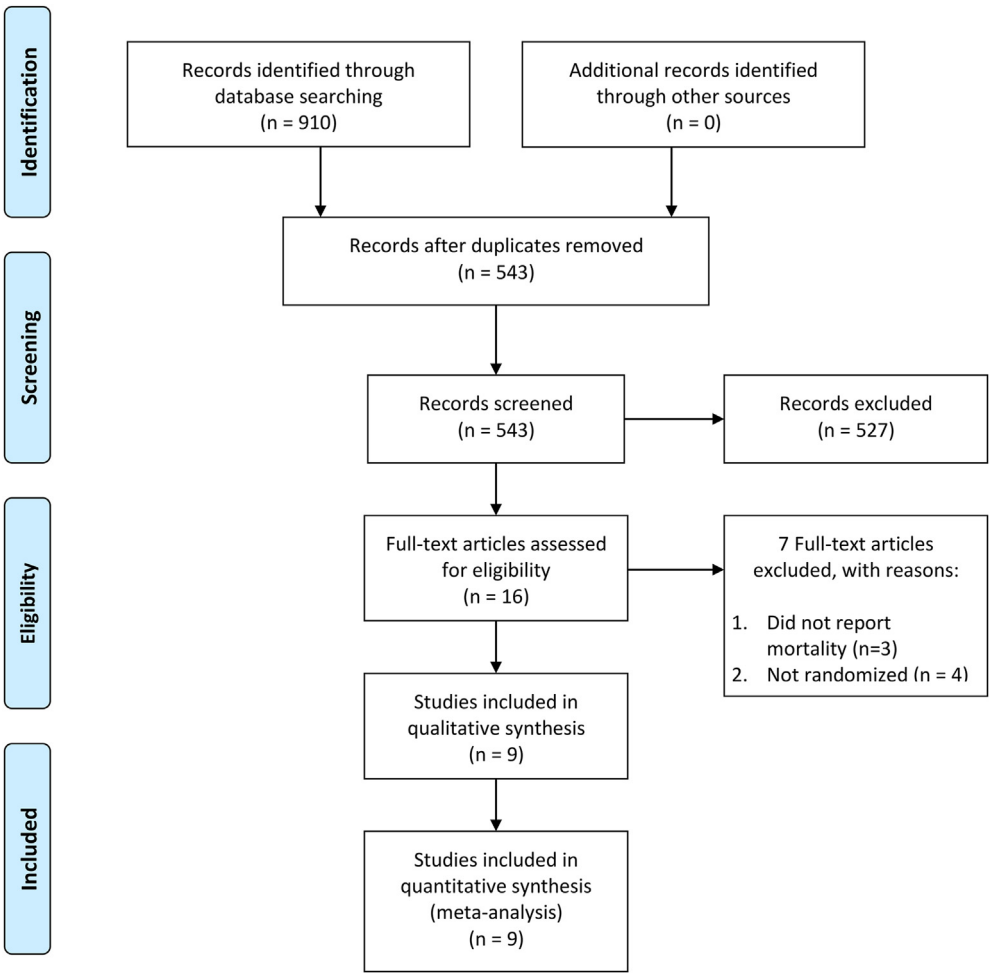

Fig. 1. Prisma flowchart.

Table 1
Baseline characteristics.

Authors	Study Design	Samples	Ivermectin Dose	Control	Severe COVID-19 (%)	Age (years)	Male (%)	DM (%)	HTN (%)	CAD (%)	Funders
Elgazzar 2020 [23]	RCT	98 vs 176	1400 mcg/kg maximum 4 tablets OD for 4 days	HCQ	50	57	70	17	14	25	None
Galan 2021 [24]	RCT	50 vs 105	14 mg OD on day 1 and 2	HCQ/CQ	100	53.4	58.2	28.1	43.4	NA	Unclear
Gonzalez 2021 [25]	RCT	36 vs. 70	<80 kg: 12 mg OD single-dose >80 kg: 18 mg OD single-dose	HCQ/ Placebo	100	53.8	62.2	33.3	32.1	NA	Unclear
Hashim 2020 [19]	RCT	70 vs 70	200 mcg/kg OD on day 1 and 2	SOC	31.4	49	52	NA	NA	NA	Unclear
Lopez-Medina 2021 [28]	RCT	200 vs 198	300 mcg/kg OD for 5 days	Placebo	0	37	42.5	5.5	13.3	NA	Centro de Estudios en Infectología Pediátrica
Niaee 2020 [20]	RCT	90 vs 90	400 mcg/kg OD (single dose or per 2 days) and 200 mcg/kg OD (single dose or per 2 days)	HCQ/ Placebo	12.2	NA	50	NA	NA	NA	Qazvin University of Medical Sciences and Science and Technology Park
Ravikitri 2021 [22]	RCT	55 vs 57	12 mg OD on day 1 and 2	Placebo	0	52.5	72.3	35.7	34.8	8.9	AIIMS, Sun Pharma
NCT04523831 [27]	RCT	183 vs 180	12 mg OD for 5 days	SOC	0	39.6					Dhaka Medical College
NCT04646109 [26]	RCT	30 vs 30	200 mcg/kg OD for 5 days	HCQ/ Favipiravir	100	62.2	66.7	31.6	45	21.7	Afyonkarahisar Health Sciences University, NeuTec Pharma

CAD: Coronary Artery Disease, COVID-19: Coronavirus Disease 2019, DM: Diabetes Mellitus, HTN: Hypertension, RCT: Randomized Controlled Trials, NA: Not Available, OD: Once Daily.

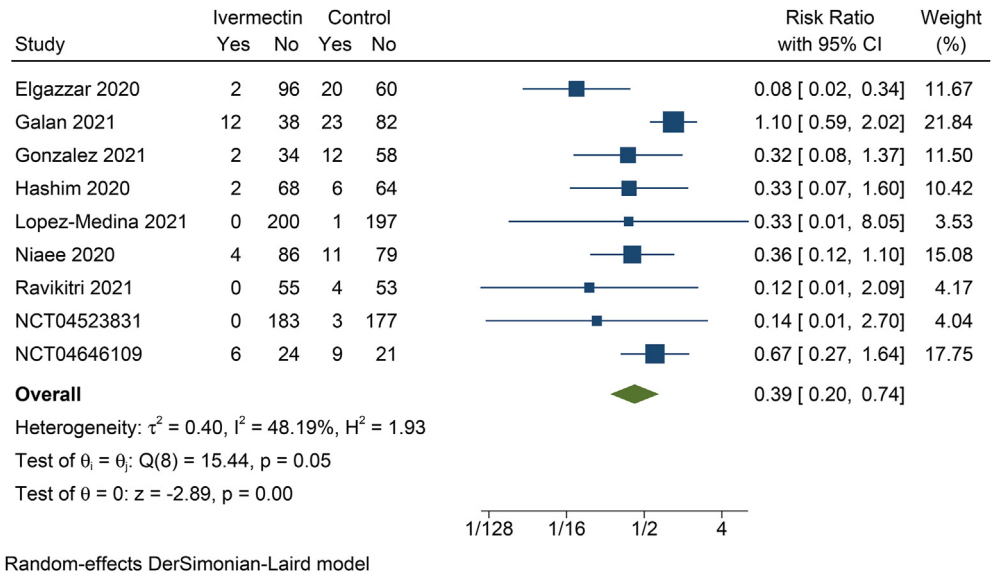

Fig. 2. Ivermectin and mortality.

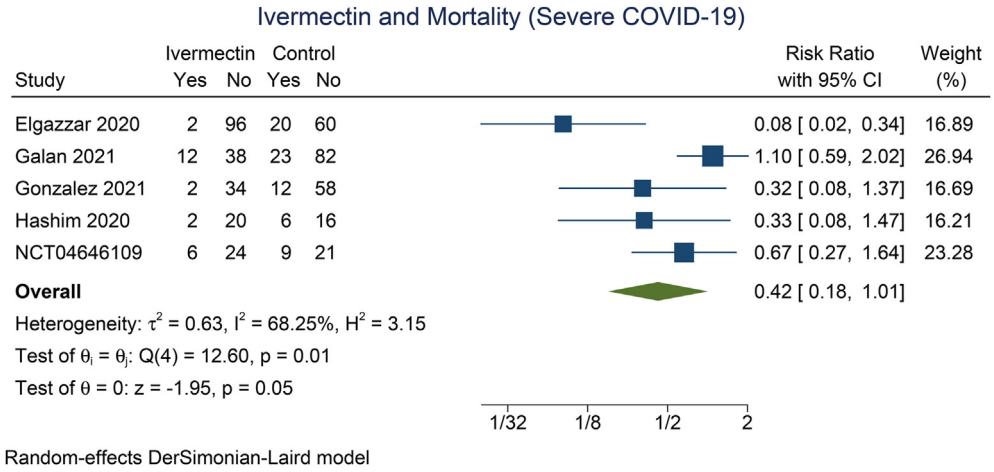

Fig. 3. Ivermectin and mortality (severe COVID-19 subgroup).

report the stage of hypertension, controlled/uncontrolled, and medications used in hypertensive patients; which may confound the association. The underlying mechanism for this observation is unclear and requires further investigation. However, this observation might be due to 100% severe COVID-19 in two studies which enroll high percentage of hypertension (Galan et al. [24] and NCT04646109 [26]), also these studies did not clearly report the presence of coronary artery disease or heart failure, which are important complications of hypertension. Thus, the finding might also be a coincidence or an indicator of other end organ complications. Interestingly, diabetes does not significantly affect ivermectin's benefit. Some antidiabetic drugs have been shown to lower mortality in COVID-19 and glucose control seemed to be an important component in these patients [31–34]. These factors were vaguely reported by the included studies and may affect the analysis.

Ivermectin is a macrocyclic lactone antiparasitic drug which is well known for its broad spectrum antiparasitic activity, high efficacy, and excellent safety profile [7,8]. Known for its versatility, ivermectin shows wide array of antimicrobial, antiviral, and anticancer activities [9–14]. Recent studies have shown that ivermectin has antiviral activity against several RNA viruses, which might be useful in combating SARS-CoV2 [15–18].

Ivermectin is a mixture of both equipotent 22,23-dihydroavermecton B1a (80%) and 22,23-dihydroavermectin B1b (20%) [7,8]. Ivermectin's potential antiviral activity against several RNA viruses including, zika virus, influenzae A virus, human immunodeficiency virus (HIV) and dengue virus has been demonstrated [18,35,36]. One of the most important antiviral mechanism is the inhibition of importin α/β1 heterodimer, which is essential for nuclear trafficking viral protein, thus important for viral replication [17,35,37]. Another possible mechanism that had been discovered in the past, but was not fully explained, is the role of ivermectin as an ionophore agent [11]. Ionophores are molecules which have both hydrophilic pockets that serve as an ion binding site, covered by hydrophobic on the external surface. These properties allow ionophore to cross across cell membrane, affecting hydro-electrolyte balance. The two structures that form ivermectin,

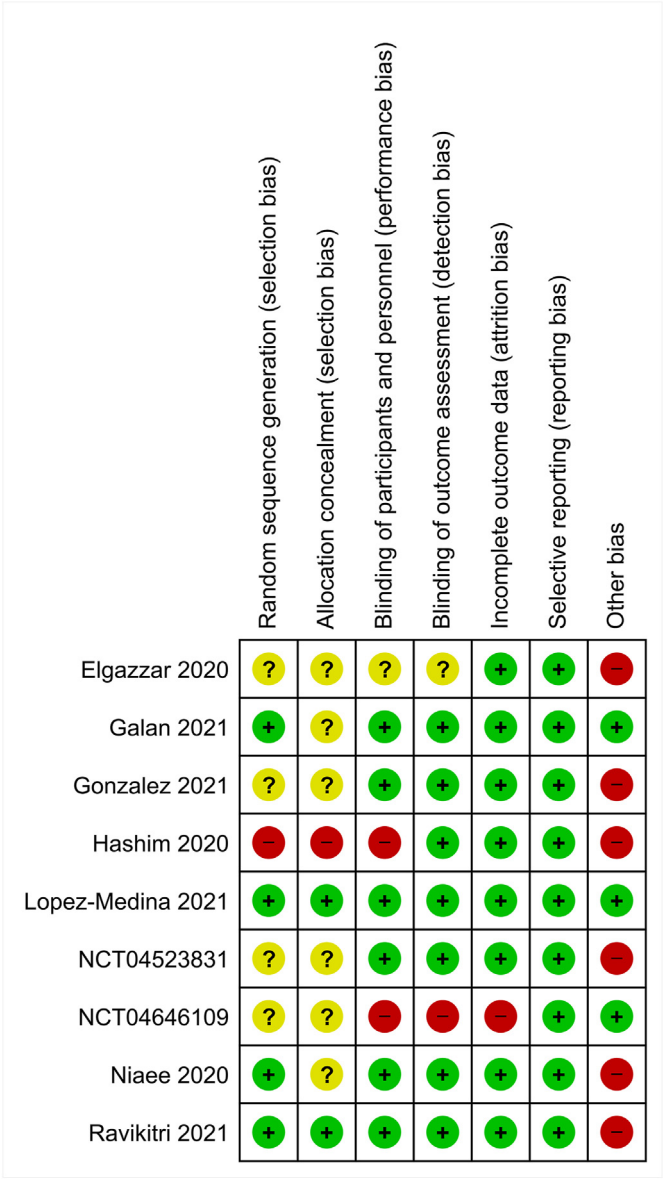

Fig. 4. Risk of bias assessment.

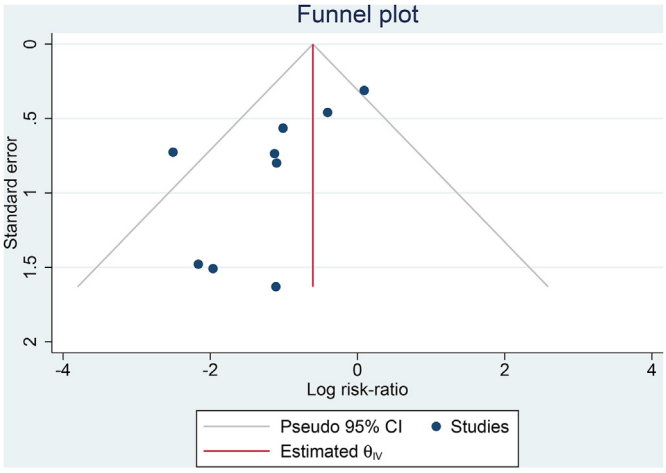

Fig. 5. Publication bias.

reacting with each other in a "head-tail" fashion. This configuration is possibly mediated by plasma transport proteins, such as albumin [38]. The conformation eventually would lead to osmotic lysis and help neutralizing the virus at an early stage of infection [39]. This mechanism is proposed to be effective in viruses without a protein capsid, which will resist osmotic lysis [7]. SARS-CoV2 is present with only a phospholipid envelope with few proteins inserted within [40].

Ivermectin also demonstrates in vivo and in vitro anti-inflammatory activities, through reducing the production of inflammatory cytokines such as TNF-alpha, interleukin-1 (IL-1) and interleukin-6 (IL-6) [41]. In mice, administration of ivermectin suppresses mucous hypersecretion and the production of inflammatory cytokines in the sample that was taken from bronchoalveolar lavage [42].

Ivermectin also appears to inhibit SARS-CoV2 replication in vitro and show a ~5000 fold reduction in viral RNA at 48 h [43]. Although the exact mechanism is not fully elucidated, it is proposed that multiple mechanisms such as inhibition of importin α/β1 heterodimer and the role of ivermectin as ionophore might contribute to its broad-spectrum antiviral activity [43,44]. Despite promising results and satisfactory safety profile, the use of ivermectin is limited to its pharmacokinetic problems such as low solubility and high cytotoxicity [45]. Therefore, more controlled studies are needed to determine the benefit of ivermectin in COVID-19.

5.1. Limitations and way forward

Most of the included studies were preprints, which is not yet peer-reviewed, and presented as a potential source of bias; this is the most important limitation of this meta-analysis. It is known that studies with positive results are likely to be published or reported, and the accuracy of meta-analysis highly depends on the source material. The presence of publication bias is also supported by the funnel-plot analysis and Egger's test. Most studies individually reported a p-value of >0.05, this might be caused by inadequately powered trial (low incidence of mortality and inadequate sample size). However, it should be noted that the only study reporting significantly lower mortality, as shown in Fig. 2, was at high risk of bias (too many uncertainties upon RoB assessment) and displayed unclear baseline characteristics among the two groups [23]. It should also be noted that the control group of the study has a higher mortality rate compared to the control group of the other studies, one of the possible explanations is due to high number of comorbidities in this group. Most of the studies also did not report important parameters such as chronic kidney disease, heart disease, medications for chronic diseases [46], and laboratory parameters such as d-dimer and c-reactive proteins which may affect prognosis. Uneven distribution of comorbidities may affect the results. Additionally, the dose and length of ivermectin administration varied across the studies.Thus adequately powered double-blinded placebo-controlled RCTs with similar baseline characteristics and dosing among the intervention and control groups are required before a definite conclusion can be made.

6. Conclusion

Ivermectin was associated with decreased mortality in patients with COVID-19 with a low certainty of evidence. Further double-blinded placebo-controlled RCTs with large samples are required for definite conclusion. In the future, if the pre-prints publication is published with the similar result to the current analyses, the certainty of evidence will increase.

Table 2
Certainty of evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivermectin	SOC	Relative (95% CI)	Absolute (95% CI)		
Mortality												
9	randomized trials	serious a	serious b	not serious	not serious	publication bias strongly suspected strong association c	28/812 (3.4%)	93/976 (9.5%)	RR 0.44 (0.25 −0.78)	53 fewer per 1000 (from 71 fewer to 21 fewer)	◯◯ LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio.
Explanations.
a. Multiple studies with high risk of bias (see Fig. 3).
b. High heterogeneity.
c. Asymmetrical Funnel Plot.

CRediT authorship contribution statement

Ahmad Fariz Malvi Zamzam Zein: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **Catur Setiya Sulistiyana:** Data curation, Investigation, Writing – original draft. **Wilson Matthew Raffaelo:** Data curation, Investigation, Writing – original draft. **Raymond Pranata:** Conceptualization, Methodology, Software, Data curation, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors have no potential conflict of interest.

ABBREVIATIONS INDEX

COVID-19	Coronavirus disease 2019
CRP	*C*-reactive protein
IF	Interferon
IL	Interleukin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
RCT	Randomized Controlled Trial
RR	Risk Ratio

Ethical approval

Not Applicable.

Funding

None.

Data availability

Data are available on reasonable request.

Informed consent

Not Applicable.

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