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Review Article

IVERMECTIN IN THE TREATMENT OF COVID-19 DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

DEWA AYU AGUS SRI LAKSEMI[1*], I. KETUT TUNAS[2], PUTU EKA WIDYADHARMA[3], WAYAN GDE ARTAWAN[4], LUH PUTU RATNA SUNDARI[5]

[1]Department of Parasitology, Faculty of Medicine, Udayana University, Jalan PB Sudirman Denpasar, Bali 80234, Indonesia, [2]Health Information Management Studi Program, Bali International University Jl. Seroja, Gang Jeruk, Kelurahan Tonja Denpasar Utara, Bali 80239, Indonesia, [3]Department of Neurology, Faculty of Medicine, Udayana University, Jalan PB Sudirman Denpasar, Bali 80234, Indonesia, [4]Department of Preventive Medicine and Public Health, Faculty of Medicine, Udayana University, Jalan PB Sudirman Denpasar, Bali 80234, Indonesia, [5]Physiology Department, Faculty of Medicine, Udayana University Jalan PB Sudirman Denpasar, Bali 80234, Indonesia

[*]Email: srilaksemi@unud.ac.id

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ABSTRACT

Objective of the review was to evaluate the effectiveness of Ivermectin as a treatment of COVID-19. The researchers collected and assessed articles and previous studies in the form of Randomized Clinical Trial (RCT) from PubMed, Google Scholar, Clinical Trials Gov and Preprint databases. The inclusion criteria of the study were the patients diagnosed with mild to moderate COVID-19 who had only been given Ivermectin compared to placebo or Standard of Cure (SoC) of COVID-19. There are 11 RCT which are resemble to the inclusion criteria of the study. Based on the 11 RCT that are suitable to the inclusion criteria of the study, the researchers found the pooled OP rate for viral load, Day to Negativity (DTN), and Escalation of Cure for all studies are 62% (95% CI, 0.50-0.74), 89% (95% CI, 0.40-1.38) and 43% (95% CI, 0.06-0.08) respectively. Moreover, the pooled OR rate for length of stay or hospitalization, mortality or deterioration, symptom reduction of all studies are 100.6% (95% CI, 0.54-1.58). Due to the lack of substantial data on information sources and low-to-moderate quality of studies which are included in systematic review, the evidence suggests that IVM (Ivermectin) administration does not decrease the mortality, symptom and viral load of COVID-19.

Keywords: COVID-19, Ivermectin, Treatment, Meta-analysis

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INTRODUCTION

More than 5 million deaths and more than 276 million confirmed cases have been caused by Novel coronavirus (SARS-CoV-2) by December 2021 [1]. COVID-19 pandemic has changed the social and economic life of people around the world [2]. Up to the present time, no standardized antiviral treatment has been found yet to overcome COVID-19 [3, 4]. Optimal supportive care remains the gold standard. Most of COVID-19 patients have mild or moderate course of disease, only 5-10% is found to have severe and fatal course of disease [5]. Individual protection, such as using masks, avoiding crowds, maintaining personal hygiene, and taking supplements, which strengthen immunity is the significant effort in preventing COVID-19 [6]. In infections caused by viruses, the most important protection is avoiding contact with patients or social distancing [4].

The effectiveness of pharmacologic treatment for COVID-19 comes with different results. The cost-effectiveness of COVID-19 drugs are vary depending on numerous factors. With an increasing number of COVID-19 cases, adequate supply of drugs for handling COVID-19 is needed especially the highly effective ones [7]. Delta variant of COVID-19 cases have been significantly increased during July to August in India, Indonesia, and several other Asian countries (WHO). Therefore, the discovery of effective drugs for COVID-19 is crucially required [5]. Several drugs such as chloroquine, hydroxychloroquine, lopinavir/ritonavir, favipiravir, remdesivir, including ivermectin are the most used agents worldwide [5]. The FDA has recommended IVM as an inhibitor of SARS CoV-2 replication *in vitro* [8]. Presently, there is no proven data on the efficacy of ivermectin against viruses *in vivo*, the use of a placebo in the control group is ethically justified [9].

Ivermectin is a member of the avermectin family produced by Streptomyces avermitilis. Ivermectin has various activities, including broad-spectrum endo/ecto-parasitic activity, antiviral, antibacterial, and anticancer activity. In 1980, Ivermectin began to be used commercially for treatment in animals. Besides being used in animal health, Ivermectin is also used in maintaining food production. In humans, Ivermectin is used to treat onchocerciasis and used as drug choice for various parasitic diseases. The mechanism of Ivermectin as an anthelmintic, involves the opening of the glutamic gate chloride channel and Gamma aminobutyric acid (GABA), resulting in an increase of chloride ion conductance which causes motor paralysis in parasites [10].

Research by Sharun *et al.*, 2020 stated that Ivermectin has been tested *in vitro* against various viruses including Zika virus [10]. In an *in vitro* study on human neural stem cells and primary amnion cells, it was found that Ivermectin was the most potent drug to inhibit Zika virus (ZIKV) infection. However, Ivermectin was failed to inhibit lethal Zika virus infection in knockout mice [11]. Yet, there have been only *in vivo* studies on the antiviral effectiveness of Ivermectin against Newcastle disease virus, West Nile virus, pseudorabies virus, and parvoviruses infections [10]. In addition, the study on Ivermectin as a DENV infection drug is currently in phase III clinical trial in Thailand in 2014–2017, with the results had showed that IVM reduces viral NS1 protein [12].

To achieve an IC50 that is effective in inhibiting SARS-CoV2 *in vitro*, 10-fold doses (120 mg) that are simulated in kinetics of Ivermectin in cattle is required. However, based on the results of pharmacokinetic studies in humans indicate that Ivermectin has a concentration 10 times higher than the reported effective concentration of 50% (EC50). Another characteristic of Ivermectin is its long half-life and is highly lipophilic with a volume of distribution (Vd) tendency to accumulate in the lungs and tissues [13].

Collectively, there are multiple pharmacodynamic and pharmacokinetic indicators that suggest a potential utility and efficacy of Ivermectin in COVID-19 [13]. Nowadays, the trend of research on COVID-19 treatment in the world shows that various countries have conducted studies on the use of Ivermectin and scientific evidence is needed to support the use of Ivermectin as a COVID-19 treatment. Thus, this study evaluated the safety and

effectiveness of Ivermectin as the treatment of COVID-19 through systematic literature review.

MATERIALS AND METHODS

This systematic review research was conducted using the Systematic-Meta Analysis (PRISMA) method.

Search strategy and inclusion criteria

The researchers searched the following database: preprint repository databases, Clinical Trial. gov, PubMed, Google scholar from January 2000 to December 2021. The references of all identified studies were also collected, as well as related review papers. The search strategies used the following terms, (SARSCoV-2) and (Ivermectin).

Studies evaluating the use of Ivermectin as treatment of mild-to-moderate COVID-19 were included. Studies that are not full text or have a sample size of<10 patients, as well as the ones evaluating Ivermectin as prophylaxis of COVID-19, were excluded. Two reviewers (EW and KT) screened the titles and abstracts of all identified studies to evaluate their eligibility for inclusion.

Data extraction and quality assessment

Data such as: first author, study region, publication year, study design, patient baseline characteristics, IVM dose, and study outcomes for each study were extracted by three researchers (SL, EW, and RS). The data extracted by researchers were only data from the ivermectin RCT that met the inclusion criteria, any disagreement among the reviewers was resolved through discussion.

Definition of outcomes

The outcomes of the study were mortality, length of hospital stay (LoS), complication or the need for mechanical ventilation, viral load, resolution of symptoms, day to negativity (DTN), and symptom reduction or adverse event (AE). Outcome, literature inclusion criteria or eligibility criteria, keyword and algorithm that had been used in this systematic review for search strategy are shown in table 1.

Table 1: Search strategy and journal inclusion criteria

Strategy	Description
Population	Patient diagnosed with COVID-19
Intervention	Ivermectin alone
Comparator	Placebo or Standard of Cure (SoC) of COVID-19
Outcomes	Mortality, Length of hospital stay (LoS), Complication or the need for mechanical ventilation or Escalation Cure, Viral load, Day to negativity (DTN), and Symptom reduction or Adverse event (AE)
Study design	Randomized Clinical trial
Eligibility criteria	The study involved adults diagnosed with mild-to-moderate infection of COVID-19. In this study, the intervention was with Ivermectin alone. Only original articles from RCT Randomized Clinical trial, blind compared to standard of cure or placebo
Restriction	English language. Peer-reviewed articles. Database from Scientific Electronic Library Online (Scielo)
Electronic database	Electronic database Medline/PubMed, Google Scholar and ClinicalTrials. gov
Focused question	Is Ivermectin effective as a treatment against mild-to-moderate COVID-19?
PubMed	(“COVID-19”[Supplementary Concept] OR “COVID-19”[All Fields] OR “covid19”[All Fields]) AND “treatment”[All Fields] AND (“ivermectin”[MeSH Terms] OR “ivermectin”[All Fields] OR PubMed“Ivermectin”[All Fields]) AND (“outcome”[All Fields] OR “recovery”[All Fields]) AND (“clinical trial”[All Fields] OR “clinical trials as topic”[MeSH Terms] OR “clinical trials”[All Fields])
Google Scholar	“COVID-19”+”treatment”+”ivermectin”+(“outcome” or “recovery”)+”clinical trial”
ClinicalTrials. gov	COVID-19 OR SARS-COV-2 | treatment | hydroxychloroquine | recovery OR outcome | Filters: Completed Studies | Results

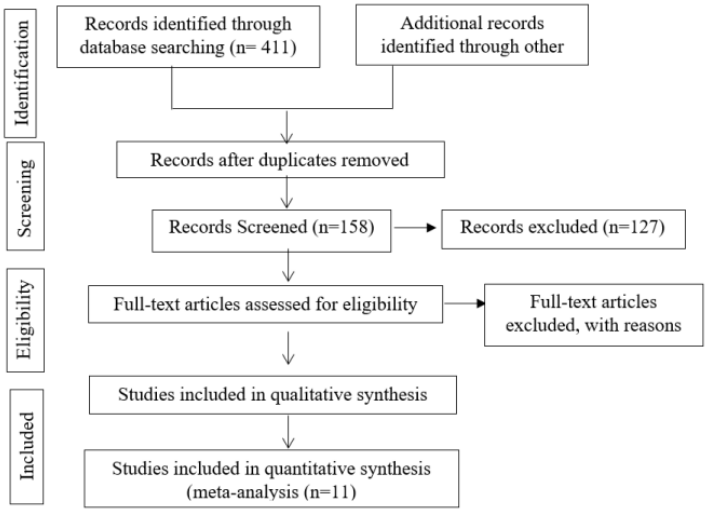

Fig. 1: **Flow diagram of the study selection process following the preferred reporting for systematic reviews (PRISMA) guideline**

Statistical analysis

The main characteristics and findings of each study were analyzed by descriptive statistics in tabular form All statistical analyses were performed using STATA SE 12.1. Statistical analysis was carried out using a forest plot or pooled estimate, and the I2 was calculated as a measure of heterogeneity between studies.

RESULTS

Search results

There were 412 citations generated from the electronic database search and manual filtering: 254 were excluded as duplicate records and 127 citations that did not meet the inclusion or exclusion criteria were

excluded: 31 potential and relevant citations were retrieved as full-text documents and examined in more detail (fig. 1). 20 text documents were issued because it was a recurring report. Finally, a total of 11 studies were obtained with 2787 patients meeting the selection criteria (table).

Characteristics of the included studies

All studies reported the outcomes of mortality, length of hospital stay (LoS), complication or the need for mechanical ventilation, viral load, resolution of symptoms, day to negativity (DTN), and symptom reduction or Adverse event (AE).

There were 11 studies which were finally analyzed. Two journals were only found to be supplementary (incomplete). There were five studies that performed standard of cure as control while the six studies performed placebo. The number of samples in the RCT was ranged from 24 to 876, while the age was from 5-82 y, the dose of ivermectin was ranged from 0.2 mg/kg BW to 0.6/kg BW, and the duration of ivermectin administration (IVM) was ranged from 1 to 5 d.

Six studies showed Ivermectin was significantly better than controls in producing the desired outcome, while others showed the opposite results. There were 5 studies showing that Ivermectin did not significantly reduce viral load, only 1 study showed otherwise. There were 3 studies showed Ivermectin significantly reduce symptoms, while 2 other studies showed the opposite.

Table 2: Summary of characteristics and results of the studies included in the review

No	Author	RCT/control/Patient covid grade	Dosage	Setting	Sample size	Result	Key outcome	Jaded score
1	Abd-Elsalam *et al.*, 2021	RCT SoC (Standard of Cure) mild to moderate Covid-19	12 mg once daily for three days	Egypt (inpatient)	164	there was no statistically significant difference in any endpoints by ivermectin; there was an observed trend to reducing hospital stay in the ivermectin	Mortality, Length of hospital stay (LoS) and the need for mechanical ventilation	3
2	Chaccour *et al.*, 2021	RCT Placebo mild to moderate Covid-19	400 mcg/kg BW (Body Weight)	Barcelona (outpatient)	24	There was no significant difference on PCR positives; tendency to symptom reduction tendency to lower viral loads and lower IgG titers	Viral load, Complication	4
3	Babalola *et al.*, 2021	RCT SoC mild to moderate Covid-19	6 mg and 12 mg	Nigeria (inpatient)	62	HR 2.38	Day to negativity (DTN), Symptom reduction and Adverse Event (AE)	4
4	Krolewiecki *et al.*, 2021	RCT SoC mild to moderate Covid-19	0.6 mg/kg/day for 5 d versus standard of care	Argentina (inpatient)	45	There was no difference in viral load reduction	Viral Load	4
5	López-Medina *et al.*, 2021	RCT Placebo mild to moderate Covid-19	300 µg/kg of body weight per day for 5 d	Colombia (Inpatient)	876	There was no significantly improve the time to resolution of symptoms.	Symptom reductions and adverse events (AE)	4
6	Shahbaznejad *et al.*, 2021	RCT SoC moderate to severe Covid-19	0.2 mg/kg	Iran (Inpatient)	96	important clinical features of COVID19 were improved with ivermectin use	LoS, Symptom reduction	
7	Kirti *et al.*, 2021	RCT Placebo mild to moderate Covid-19	Dosage 12 mg days 1, 2.	India (Inpatient)	112	There was no difference in the primary outcome i.e. negative RT-PCR status on day 6 of admission with the use of ivermectin.	Symptom reductions. LoS, Complication/mechanical ventilation	3
8	Bukhari *et al.*, 2021	RCT SoC mild to moderate Covid-19	12 milligrams	Pakistan (Inpatient)	86	Eearly viral clearance was observed and no side effects were documented.	Viral Load, DTN, Adverse event (AE)	3
9	Samaha *et al.*, 2021	RCT Placebo mild to moderate Covid-19	150µg/kg body weight of ivermectin, maximum dose 400 ug/kg	Lebanon (outpatien)	100	Ivermectin appears to be efficacious in providing clinical benefits in a randomized treatment of asymptomatic SARS-CoV-2-positive subjects	Symptom reduction, Viral Load, LoS (quarantine duration) AE	3
10	Chasidow *et al.*, 2021	RCT placebo mild Covid-10	0,3 mg/kg BW for 5 d	Cali Colombia (Inpatient)	476	Usefulness of IVM for treatment of mild COVID-19 was not demonstrated.	resolution of symptoms escalation of care	4
11	Biber *et al.*, 2021	RCT Placebo mild to moderate Covid-10	0.2 mg/kg for 3 d vs. placebo in non-hospitalized COVID-19 patients	Israel (Inpatient)	89	There were significantly lower viral loads and viable cultures in the ivermectin group	Viral Load	5

Outcomes

The pooled OR for viral load, day to negativity (DTN), escalation of cure for studies reporting these data were 62% (95% CI, 0.50-0.74), 89% (95% CI, 0.40-1.38), 43% (95% CI, 0.06-0.08) respectively (fig. 2, 3 and 4). The pooled OR for length of stay or hospitalization, mortality or deterioration, symptom reduction for three studies reporting these data were 100.6% (95% CI, 0.54-1.58), 100.09% (95% CI, 0.99-1.19),95% (95% CI, 0.83-1.08),respectively (fig. 5, 6 and 7).

Test for heterogeneity were found: $\chi 2$ =33.19, df=3, p=0.000, I^2 =91% while test of overall effect: z= 9.93, p = 0.000. The effect of ivermectin administration in COVID-19 patients on viral load showed that there was a high variation on the results of previous studies, and those variation were statistically significant.

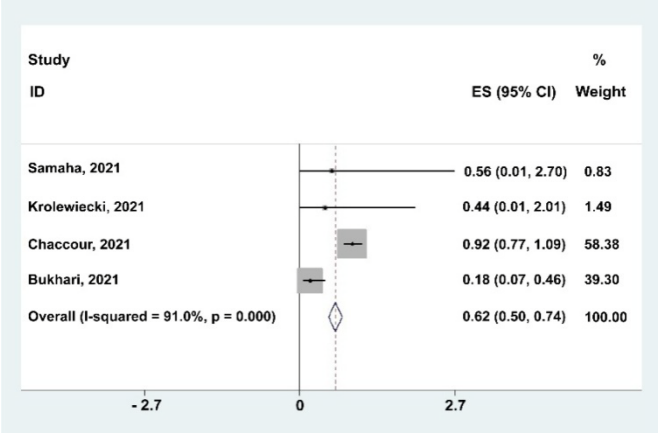

Fig. 2: The pooled viral load OR for COVID-19 patient who received ivermectin treatment

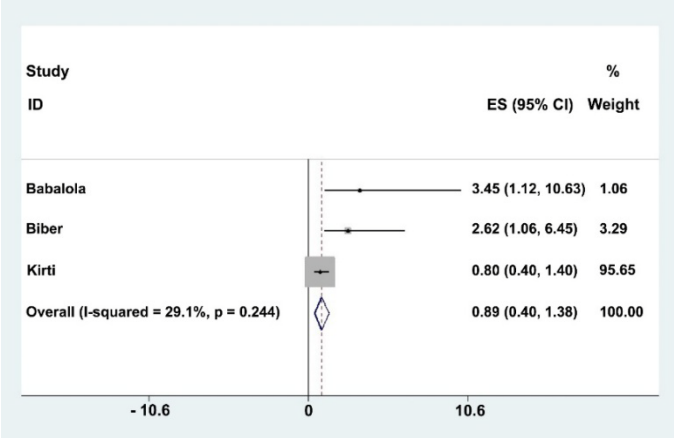

Fig. 3: The pooled day to negativity (DTN) OR for COVID-19 patient who received ivermectin treatment

Test for heterogeneity were found: $\chi 2$ =2.82, df=3, p=0.000, I^2 =29.1% while test of overall effect: z= 3.56, p = 0.000. The pooled OR at Day to Negativity for three studies reporting these data were 89% (95% CI, 0.40-1.38). Heterogeneity or variation between studies that investigated the effect of ivermectin administration in COVID-19 patients on day to negativity (DTN) was statistically significant.

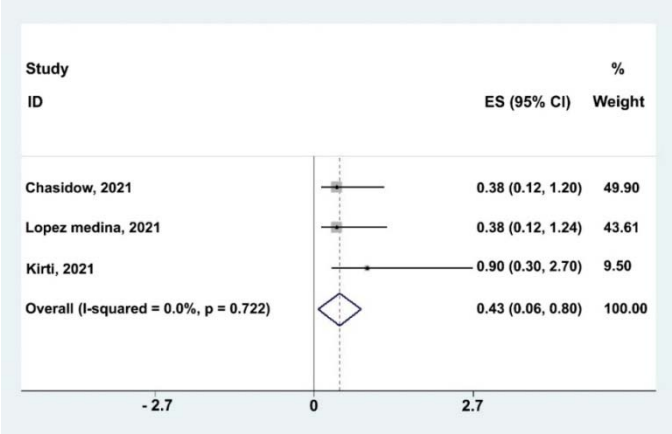

Fig. 4: The pooled escalation cure OR for COVID-19 patient who received ivermectin treatment

Test for heterogeneity were found: $\chi 2$ =0.65, df=2, p=0.722, I^2 =0% while test of overall effect: z= 2.28, p = 0.023. The pooled OR for escalation of cure for three studies reporting these data were 43% (95% CI, 0.06-0.08). Heterogeneity or variation between studies that investigated the effect of ivermectin administration in COVID-19 patients on day escalation of cure was statistically significant.

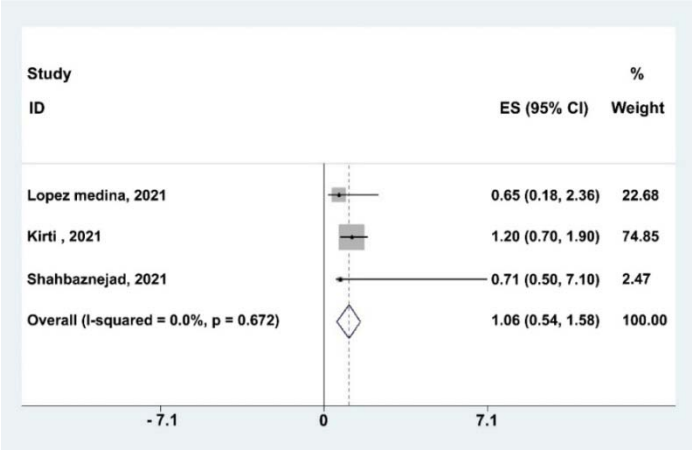

Fig. 5: The pooled length of stay (LoS) or hospitalization OR for COVID-19 patient who received ivermectin treatment

Test for heterogeneity were found: $\chi 2$ =0.79, df=2, p=0.672, I^2 =0% while test of overall effect: z= 4.01, p = 0.000. The pooled OR for length of stay or hospitalization for three studies reporting these data were 100.6% (95% CI, 0.54-1.58). Heterogeneity or variation between studies that investigated the effect of ivermectin administration in COVID-19 patients on length of stay or hospitalization was statistically significant.

Test for heterogeneity were found: $\chi 2$ =1.59, df=2, p=0.451, I2 =0% while test of overall effect: z= 21.58, p = 0.000. The pooled OR for mortality or deterioration for three studies reporting these data were 100.09% (95% CI, 0.99-1.19). Heterogeneity or variation between studies that investigated the effect of ivermectin administration in COVID-19 patients on mortality or deterioration was statistically significant.

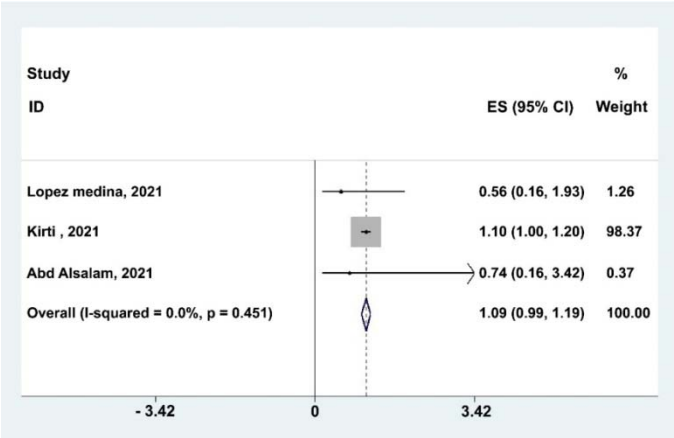

Fig. 6: The pooled mortality or deterioration OR for COVID-19 patient who received ivermectin treatment

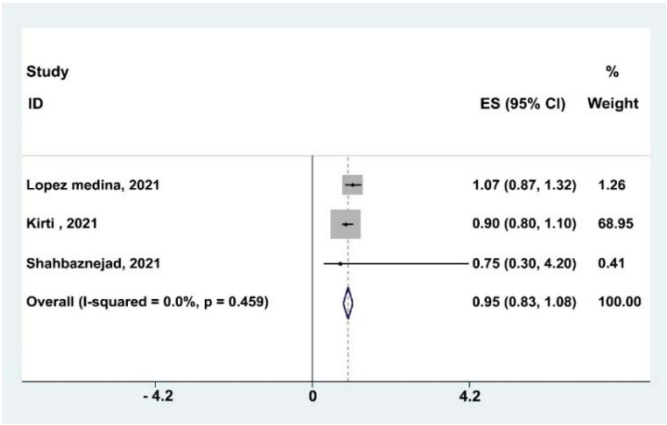

Fig. 7: The pooled symptom reduction or for COVID-19 patient who received ivermectin treatment

Test for heterogeneity were found: $\chi 2$ =1.56, df=2, p=0.459, I2 =0% while test of overall effect: z= 14.97, p = 0.000. The pooled OR for symptom reduction for three studies reporting these data were 95% (95% CI, 0.83-1.08). Variation between studies that investigated the effect of ivermectin administration in COVID-19 patients on symptom reduction might not be important but statistically significant.

Based on the above analysis, this meta-analysis shows evidence with low certainty suggesting that ivermectin reduces COVID-19 infection (viral load) and the need for mechanical ventilation or an escalation cure, there may be no benefit of ivermectin to reduce mortality, day to negativity, length of stay (LoS) or hospitalization and symptom reduction.

Safety

Four studies reported mild adverse events, most of which were diarrhea, rash, nausea and headache, while two studies reported severe adverse event such as hyponatremia and multiorgan failure probable due to escalation of their covid.

Table 3: Adverse event reported by studies included in the review

No	Author	Adverse event
1	Biber *et al.*, 2021	diarrhea and rash resolved in two days
2	Babalola *et al.*,2021	No adverse effects of Ivermectin was reported
3	Abd Alsalam *et al.*, 2021	Mild side effects were recorded; diarrhea and nausea
4	Bukhari *et al.*, 2021	no potential adverse reaction were noted
5	Chaccour *et al.*, 2021	There were no severe adverse events
6	Kirti *et al.*, 2021	no report
7	Chasidow *et al.*, 2021	no report
8	Krolewiecki *et al.*, 2021	mild rash and nausea, hyponatremia
9	Lopez medina *et al.*, 2021	The most common solicited adverse event was headache while the most common serious adverse event was multiorgan failure
10	Samaha *et al.*, 2021	Moreover, no adverse effects were detected at any of the tested doses
11	Shahbaznejad *et al.*, 2021	No potential adverse events, including wheezing, itching, skin rash, edema, hypotension or liver toxicity were observed in the patients of either group

DISCUSSION

Ivermectin has been discovered for 50 y ago and has used for the treatment of parasitic diseases such as onchocerciasis (river blindness), ascariasis, trypanosomiasis, malaria, head lice, scabies, and leishmaniasis [24, 25]. Besides having antiparasitic activity, ivermectin, it also exhibits antibacterial and anticancer activities [25]. Although there is no scientific evidence that ivermectin can be used as an *in vivo* treatment, in Brazil and most Latin American (LATAM) and Caribbean countries have prescribed ivermectin for the preventive treatment of severe acute respiratory syndrome coronavirus (SARS-CoV-2) soon after the publication of *in vitro* effect against viruses [24].

There is a study which suggests that a meta-analytic result and its implications depend on how to handle clinical heterogeneity. In a meta-analysis with high heterogeneity, several analytical strategies and other valid interpretations are needed to be able to conclude and believe in the results of a meta-analysis [26]. Therefore, in addition to measuring the values of X2 and I2, this meta-analysis also measures the random effects model that establishes a 95% confidence interval.

Based on a random-effects model yielding 95% CI, this meta-analysis presents evidence with low certainty showing that ivermectin reduces COVID-19 infection (viral load) by an average of 62% (95% CI 50%–74%). This results equally to Bryant 2021 that showing low-certainty evidence that ivermectin prophylaxis reduces COVID-19 by an average of 86% (95% confidence interval 79%-91%).

This meta-analysis presents evidence with low certainty that ivermectin reduces the need for mechanical ventilation or escalation cure, but there may be no benefit of ivermectin for reducing day to negativity, length of stay (LoS) or hospitalization and symptom reduction, on the contrary Bryant, 2021 mentioned that there was no benefit with ivermectin for "necessity of mechanical ventilation, but the effect estimates for "improvement" and "reduction" clearly supported the use of ivermectin [25]. Meta-analysis by Roman suggested that IVM did not reduce all-cause mortality, length of stay or viral clearance in RCTs in COVID-19 patients with mostly mild disease [28].

In this review, there were three studies with small sample sizes [13, 15, 20], while eight studies had a sufficient number of participants to be considered an appropriate sample. This meta-analysis shows that among studies examining the administration of ivermectin in COVID-19 patients, there is substantial clinical heterogeneity. The causes of heterogeneity, in addition to clinical differences, can include methodological problems such as problems with randomization, early termination of trials, use of absolute rather than relative risk measures, and publication bias [29]. In this review heterogeneity is due to the varying number of samples [15, 17].

The heterogeneity in this review is not only due to variation in the controls used, namely placebo and standard of cure (SoC), but also due to the variation in the outcomes measured, namely mortality, length of hospital stays (LoS), the need for mechanical ventilation or escalation cure, viral load, day to negativity (DTN), symptom reduction or adverse event (AE).

Another factor that causes heterogeneity in this study is the criteria for inpatient or outpatient patients and the different degrees of COVID. There are 9 studies using inpatient samples, only 2 studies took samples from outpatients. There were 10 studies that used patients with mild to moderate COVID-19, while only 1 study that used patients with moderate to severe COVID-19 [18].

Variation in studies that examined the effect of ivermectin on COVID-19 was found between placebo and standard cure (SoC). Drugs such as hydroxychloroquine [30, 31], Azithromycin [25, 30, 31], zinc [25], Vitamin C [25], Vitamin D [25] were used as standard of treatment (SoC) for the control group.

The number of samples in this RCT ranged from 24 to 876, while the age ranged from 5-82 y. regarding the intervention, almost all studies the administration of IVM was in variable doses, the dose of ivermectin ranged from 0.2 mg/kg BW to 0.6/kg BW. Duration of Ivermectin varied from single dose to five days administration.

Four studies reported mild adverse events, most of which were diarrhea, rash, nausea and headache, while two studies reported severe adverse event such as hyponatremia and multiorgan failure. These results are in contrast to the Bryant and Roman studies which showed severe side effects were rare among treatment trials [27, 28].

The studies that reported severe adverse events [16, 17] argue that the cause of hyponatremia and multiorgan failure cannot be ascertained caused by IVM, because in COVID-19 can also be found conditions of hyponatremia and multi-organ failure, so it can be concluded that hyponatremia and multi organ failure a probable due to escalation of their covid.

The mechanism of action of ivermectin as an antiparasitic is by increasing the activity of GABA receptors or glutamate gate chloride ion channels in parasites and worms that block signals between neurons

and muscles. Ivermectin also has a modulating effect on the host immune system through neutrophil activation, increased C-reactive protein and interleukin-6 levels. There are four hypotheses regarding mechanism of action of ivermectin as an antiviral: by inhibiting the nuclear import of proteins of the virus; inhibiting the import of IMPα/β1 which is required for viral RNA during infection; affecting CD147 which is the key binding site for the SARS-CoV-2 spike protein; having an ionophore role that has established as antiviral [25].

The side effects of ivermectin in vertebrates and invertebrates are different, this is because in vertebrates, mammalian GABA sensitive neurons are protected by the blood brain barrier (BBB) thereby preventing the side effects of ivermectin in vertebrates, whereas in invertebrates the risk of severe side effects is in the form of somatic muscle paralysis with movement. Sluggishness, uncoordinated coordination, starvation due to inhibited pharyngeal pumping, and death. All of these due the wide distribution of chloride ion channels in invertebrates triggers an influx of chloride ions which causes hyperpolarization and inhibits phosphorylation of the myosin II light chain [25].

There were eleven RCTs (n=1811) studies which were finally analyzed because two journals were only found to be supplementary, not complete journals. There were five studies that performed standard of cure as control while six studies performed placebo. COVID-19 disease severity in this meta-analysis was mild to moderate in ten RCTs, moderate to severe in one RCT while in other meta-analisis, ten RCTs (n=1173) were included, controls were standard of care [SOC] in five RCTs and placebo in five RCTs, while COVID-19 disease severity was mild in one RCTs, severe to moderate in one RCTs, and mild and moderate in nine RCTs [32].

There were six studies showing that ivermectin was significantly better than controls in producing the desired outcome, while the rest showed the opposite result. There were five studies showing that ivermectin did not significantly reduce viral load, only one study showed otherwise. There are three studies that show ivermectin significantly reduces symptoms, while two other studies show the opposite. This result is different from Popp 2021 which shows that from fourteen studies there are no study comparing ivermectin to an intervention with proven efficacy [33].

This research is in line with Popp and Roman's showing uncertain results about the efficacy and safety of ivermectin used to treat or prevent COVID-19. Limitation of this study was the number of RCTs that met the inclusion criteria was small, heterogeneity was found in terms of the number of samples, controls used, different outcomes. This result is also in line with other studies [32, 33].

CONCLUSION

Based on the description above, it has been found that heterogeneity or variation between studies that investigated the effect of Ivermectin administration in COVID-19 patients on mortality or deterioration was statistically significant. This meta-analysis presents evidence with low certainty that Ivermectin reduces the need for mechanical ventilation or escalation cure. Yet, Ivermectin may not benefit from reducing day to negativity (DTN), length of stay (LoS) and symptom reduction. This research also showed uncertain results about the efficacy and safety of Ivermectin used to treat or prevent COVID-19. Therefore, there is no sufficient evidence to support the use of Ivermectin in treating COVID-19 due to variation in results between studies.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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