

## The Effectiveness of Ivermectin on the Risk of Mortality in COVID-19 Patients: A Meta Analysis

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### ABSTRACT

**Background:** The Coronavirus Disease 2019 (COVID-19) has become the highest priority of global pandemic. New and repurposed drugs are being tested on mild to moderate levels of COVID-19 to help suppress transmission of the virus. Ivermectin is one of the repurposed drugs with known safety records with more than 2.5 billion doses dispensed in the past. This study aims to estimate the effectiveness of ivermectin in reducing the risk of mortality in COVID-19 patients based on the results of a number of previous similar studies.

**Subjects and Method:** This study is a systematic review and meta-analysis. This study used secondary data in the form of data from previous study results. A systematic and comprehensive database search was carried out through several databases including: PubMed, Science Direct, Google Scholar, and Springer Link. Analysis of this study was using RevMan 5.3 software. This study used the eligibility criteria with the PICO model, populations: covid-19 patients, intervention: ivermectin administration, comparison: patients without ivermectin, outcome: mortality in COVID-19 patients. The inclusion criteria used were full paper in English and Indonesian with a randomized controlled trial, including the number of deaths, and the primary study was conducted in a hospital. The keywords used to search the database were “ivermectin” AND “COVID-19” OR “SARS-COV-2” AND “mortality” OR “death” AND “randomized controlled trial”. Meta Analysis using RevMan 5.3 with Fixed Effect Model (FEM).

**Results:** Based on the results of the analysis, there is homogeneity of data between studies ( $I^2=0\%$ ;  $p=0.940$ ) so that the Fixed Effect Model (FEM) is used. The use of ivermectin in COVID-19 patients reduced the median risk of death by 0.46 times compared to patients who were not given ivermectin (aOR= 0.46; CI 95%= 0.29 to 0.72;  $p<0.001$ ).

**Conclusion:** Ivermectin is effective in reducing the average risk of mortality in COVID-19 patients.

**Keywords:** COVID-19, Ivermectin, Mortality

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### BACKGROUND

Coronavirus disease 2019 (COVID-19), caused by the new acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has

become the highest priority global pandemic. The number of cases in the world has more than 200 million people and about 5 million people have died (Johns Hopkins

University of Medicine, 2021). Indonesian data shows more than 4 million cases of COVID-19, around 100 thousand died (COVID-19 Task Force, 2021). Several types of corona-virus are known to cause respiratory tract infections in humans ranging from coughs and colds to more serious ones such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). A new type of coronavirus that was found is the cause of COVID-19 disease. COVID-19 is an infectious disease caused by a newly discovered type of coronavirus. This new virus and the disease it causes were unknown before the outbreak began in Wuhan, China, in December 2019 (WHO, 2021).

Available data suggest that a third of SARS-CoV-2 infections are asymptomatic, but uncertainty remains. Approximately 80% of symptomatic cases present with mild symptoms, including cough, fever, myalgia, headache, dyspnea, sore throat, diarrhea, nausea and vomiting, and loss of smell and taste. Outpatient management is appropriate for most people with mild COVID-19. Moderate, severe, and critical cases (approximately 20%), with the need for oxygen supplementation, ventilatory support, or intensive medical care therapy, place a considerable burden on the health care system (Huang et al., 2020; WHO, 2021).

New and repurposed drugs are being tested on mild to moderate levels of COVID-19 to help in suppressing the transmission of the virus and prevent disease progression. Ivermectin is one of the repurposed drugs with known safety records with more than 2.5 billion doses dispensed in the past. Originally introduced as an anthelmintic agent, it has recently been found to have antiviral, anti-inflammatory and anti-cancer actions as well. Laboratory testing shows that ivermectin

can slow the reproduction of the COVID-19 virus (SARS-CoV-2) but this needs further research in humans (Caly et al., 2020).

Ivermectin may be safe, affordable, and available. Therefore, the use of ivermectin guarantees rapid implementation of controlled clinical trials to assess efficacy on SARS-CoV-2. There are observational studies showing the beneficial effects of ivermectin in the treatment of COVID-19 (Alam et al., 2020).

Meta-analysis studies are epidemiological studies that statistically combine the results of a number of primary studies that can be combined to obtain a quantitative overview (Huque, 1988; Greenhalgh, 1997; Last, 2001; Delgado-Rodriguez, 2001 in Murti 2018). This study aims to estimate the effectiveness of ivermectin in reducing the risk of mortality in COVID-19 patients based on the results of a number of previous similar studies.

## SUBJECTS AND METHOD

### 1. Study Design

This is a systematic review and meta-analysis study. This study used secondary data in the form of data from the results of previous studies. This study was conducted by searching and selecting data from the results of clinical trials conducted around the world with different ethnicities, races, and locations. Filtering articles using PRISMA flow diagrams. Systematic and comprehensive database searches were carried out through several of them: PubMed, Science Direct, Google Scholar, and Springer Link between 2020 and 2021. The keywords used to search the database were “ivermectin” AND “COVID-19” OR “SARS-COV-2” AND “mortality” OR “death” AND “randomized controlled trial”.

### 2. Inclusion Criteria

The inclusion criteria in this study were full paper articles, appropriate titles, articles

selected depending on ivermectin which affects the incidence of death in patients with COVID-19, randomized controlled trials studies, articles published in English and Indonesian.

### 3. Exclusion Criteria

The exclusion criteria in this study were articles that did not include the number of deaths, articles before 2020, the control group was not patients without ivermectin administration.

### 4. Definition of Operational Variables

Search articles using the eligibility criteria with the PICO model. Populations: COVID-19 patients. Intervention: administration of ivermectin. Comparison: patients without ivermectin. Outcome: Death in COVID-19 patients.

#### Ivermectin

It is an antiparasitic agent belonging to the avermectins group, originally a fermentative metabolite produced by the bacterium *Streptomyces avermitilis*. Instruments: published articles. Measurement scale: categorical

#### Death of COVID-19 Patients

It is when the function of the heart system, circulation, and respiratory system is proven to have stopped permanently. The focus in this study is the number of deaths in COVID-19 patients. Instruments: results on published articles. Measurement scale: categorical. Measuring results: dead and not dead

### 5. Study Instruments

This study used PRISMA Flow Diagrams and study quality used a critical appraisal checklist for randomized controlled studies published by CEBM University of Oxford 2014 (CEBM, 2014).

### 6. Data Analysis

Data analysis in this study used the Review Manager application (RevMan 5.3). Forest plots and funnel plots were used to determine the effect size and heterogeneity of the

data. The fixed effect model is a statistical model used to combine the effects of various studies in a meta-analysis that assumes homogeneity of effects across the combined studies. Meanwhile, the random effect model is a statistical model used to combine the effects of various studies in a meta-analysis where heterogeneity between studies is included in the combined estimate by including the variance between studies (Delgado-Rodriguez, 2001 in Murti, 2018).

## RESULTS

The article search process is carried out by identifying articles from 2020 to 2021 using a database search engine consisting of: PubMed, Science Direct, Google Scholar, and Springer Link. The keywords used to search the database were “ivermectin” AND “COVID-19” OR “SARS-COV-2” AND “mortality” OR “death” AND “randomized controlled trial”.

The article review process can be seen in Figure 2. The results of the article search found 1,261 articles that were identified, then the multiple data was removed by 298 articles, then 963 articles were filtered. Based on the filtered articles, there were 936 articles issued and 32 articles were found that were considered eligible. Several full text articles after the assessment did not fulfill the requirements because the comparison in studies contained ivermectin, the outcome of the study was not appropriate, such as length of healing time, length of time hospitalized, reduced virus in the patient's body, severity in patients and others.

The articles that fulfilled the qualitative requirements were reviewed again and the researcher found 2 articles that did not fulfill the requirements in the presence of a combination of ivermectin with other drugs in the intervention group and did not

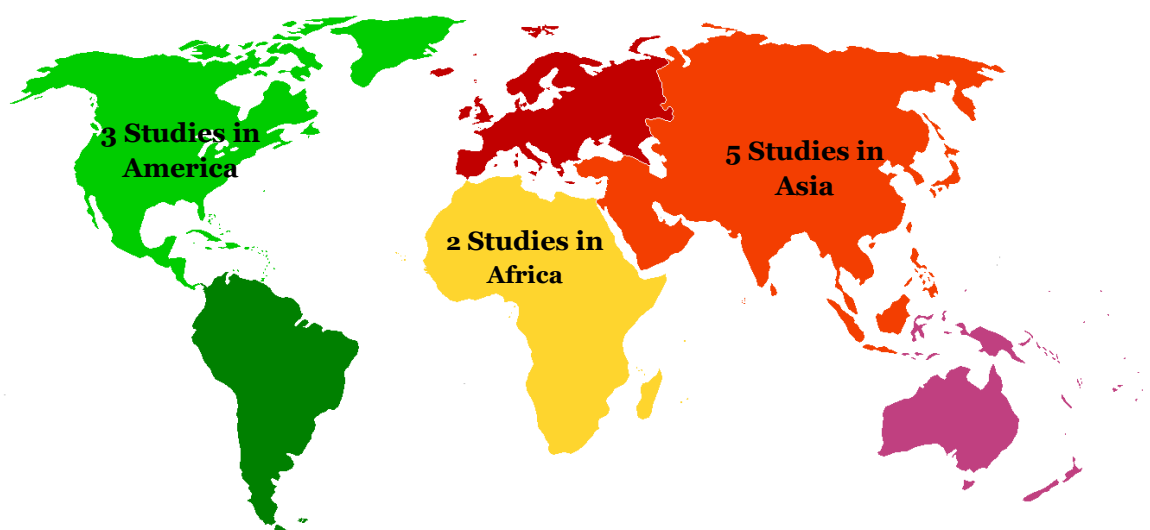
include the number of mortality. The final result of the article review showed that there were 10 articles that fulfilled the quantitative requirements for meta-analysis.

Articles obtained from the results of the review are research originating from several countries, which can be seen in Figure 1. The results of the assessment of study quality are guided by the critical appraisal tools Randomized Controlled Trials (RCT) published by the Critical Appraisal Skills Program. This study has a strong quality, it can be seen in Table 1.

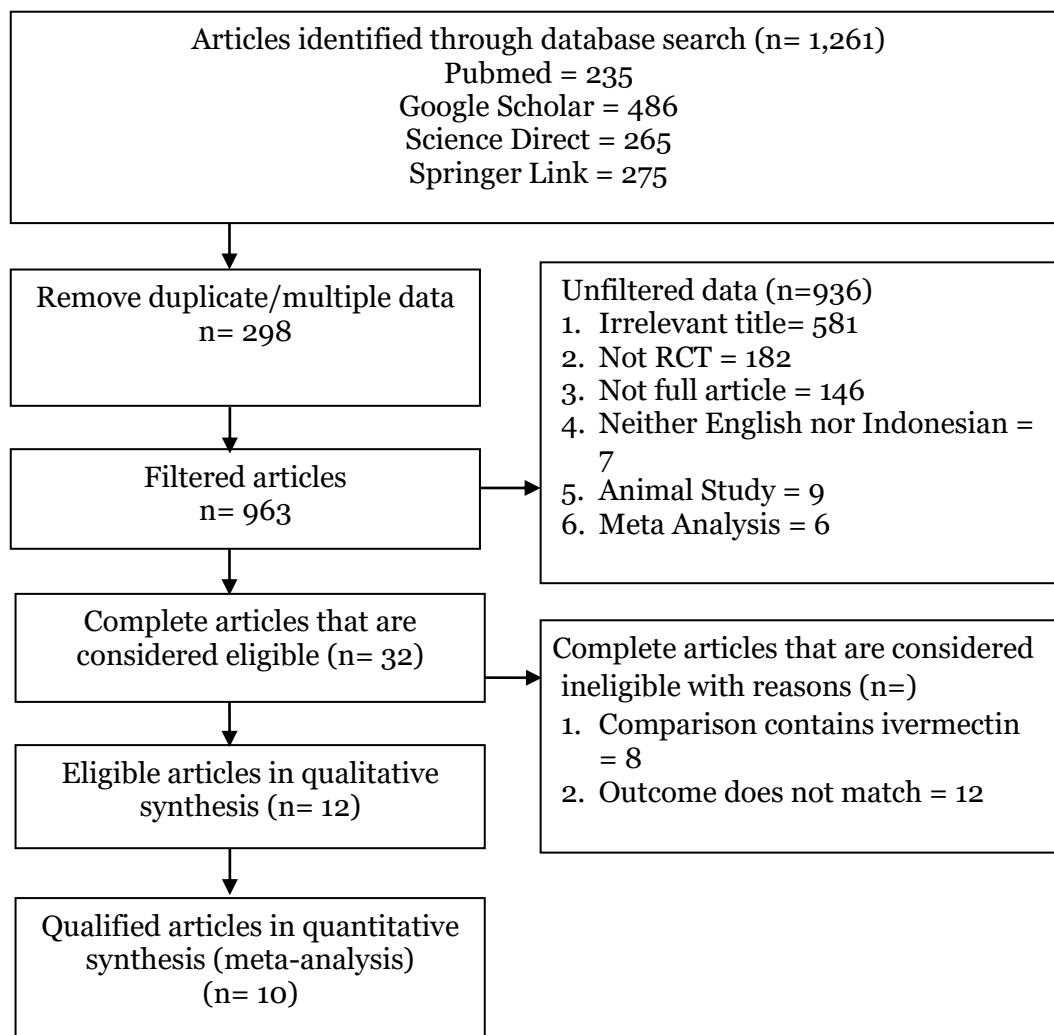
The results of the meta-analysis are presented in the form of a forest plot. The Forest Plot is a diagram showing information from each of the studies and an estimate of the overall results. In addition to the forest plot, this meta-analysis also presents a funnel plot, which is a diagram that illustrates the possibility of publication bias by showing the relationship between the study effect size and the sample size of the various studies being studied. The existence of publication bias in the funnel plot can be assessed by looking at the asymmetry of the funnel shape, the number of points on the right and left sides

compared to the standard error (Murti, 2018). There were 10 articles identified from the results of the review that fulfilled the requirements as a source of meta-analysis of the effectiveness of using ivermectin on mortality in COVID-19 patients. An overview of each study can be seen in Table 2.

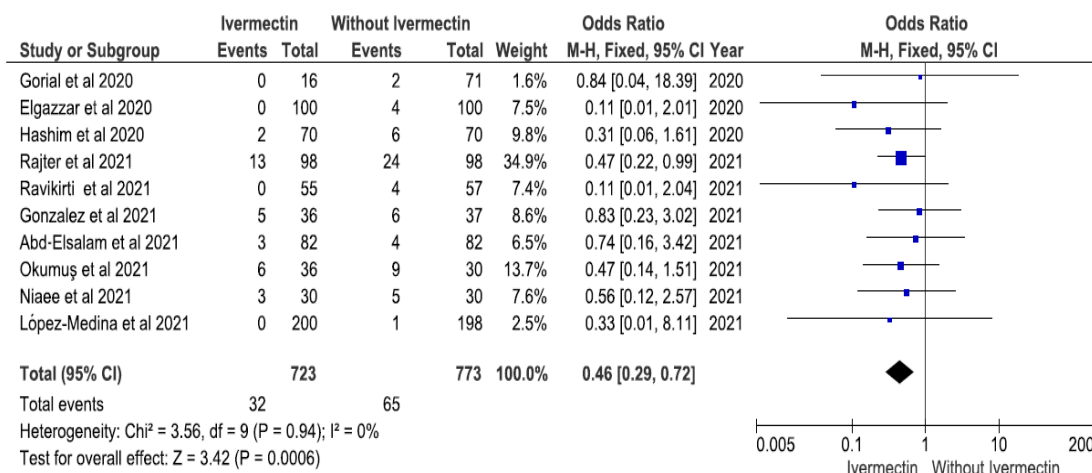
Based on the results of the analysis in Figure 3, it can be seen that there were 10 articles which reported that the administration of ivermectin could reduce the average mortality in COVID-19 patients. Based on the results of the analysis, there was no heterogeneity ( $I^2 = 0\%$ ;  $p = 0.940$ ) so the Fixed Effect Model (FEM) was used. The use of ivermectin in COVID-19 patients reduced the median risk of death by 0.46 times compared with patients not given ivermectin (aOR= 0.46; 95% CI= 0.29 to 0.72;  $p < 0.001$ ). Based on Figure 4 funnel plot of the effectiveness of ivermectin use on mortality in COVID-19 patients, the plots on the right and left sides are symmetrical to each other and form an inverted funnel. The left-right plot has a standard error of  $< 0.5$  and has a standard error of  $> 1.5$ , this indicated that there was no publication bias in this study.



**Figure 1. Map of Study Areas on the Effectiveness of Ivermectin Use on Mortality in COVID-19 Patients**



**Figure 2. PRISMA flow diagrams The Effect of Residence on the Risk of Anxiety and Depression in the General Population During the COVID-19 Pandemic**



**Figure 3. Forest Plot of the Effectiveness of Ivermectin Use on Mortality in COVID-19 Patients**

**Table 1. Critical Appraisal Checklist Effectiveness of Ivermectin Use on Mortality in COVID-19 Patients**

No	Checklist Questions	Publication (Author and Year)				
		Abd-Elsalam et al, 2021	Elgazzar et al, 2020	Gonzalez et al, 2021	Gorial et al, 2020	Hashim et al, 2020
1	Does the research address clearly focused statements/problems?	1	1	1	1	1
2	Is the Randomized Controlled Trials (RCT) method appropriate to answer the study question?	1	1	1	1	1
3	Are there enough subjects in the study to establish that the findings did not occur by chance?	1	1	1	1	1
4	Are subjects randomly allocated to the experimental group and the control group? If not can this be biased?	1	1	1	1	1
5	Are inclusion/exclusion criteria used?	1	1	1	1	1
6	Are the two groups comparable at the start of the study?	1	1	1	1	1
7	Are objective and unbiased outcome criteria used?	1	1	1	1	1
8	Are objective and validated measurement methods used in measuring the results? If not, are results judged by someone who is not aware of the group assignment (i.e. is the assessment blinded?)	1	1	1	1	1
9	Is effect size practically relevant?	1	1	1	1	1
10	How precise is the estimate of the effect? Is there a confidence interval?	1	1	1	1	1
11	Could there be confounding factors that have not been taken into account?	1	1	1	1	1
12	Can the results be applied to your research?	1	1	1	1	1
<b>Total</b>		<b>12</b>	<b>12</b>	<b>12</b>	<b>12</b>	<b>12</b>

Description:

1: Yes

0: No

**Continuation**

No	Checklist Questions	Publication (Author and Year)				
		López-Medina et al, 2021	Rajter et al, 2021	Okumuş et al, 2021	Ravikirti et al, 2021	Niaee et al, 2021
1	Does the research address clearly focused statements/problems?	1	1	1	1	1
2	Is the Randomized Controlled Trials (RCT) method appropriate to answer the research question?	1	1	1	1	1
3	Are there enough subjects in the study to establish that the findings did not occur by chance?	1	1	1	1	1
4	Are subjects randomly allocated to the experimental group and the control group? If not can this be biased?	1	1	1	1	1
5	Are inclusion/exclusion criteria used?	1	1	1	1	1
6	Are the two groups comparable at the start of the study?	1	1	1	1	1
7	Are objective and unbiased outcome criteria used?	1	1	1	1	1
8	Are objective and validated measurement methods used in measuring the results? If not, are results judged by someone who is not aware of the group assignment (i.e. is the assessment blinded?)	1	1	1	1	1
9	Is effect size practically relevant?	1	1	1	1	1
10	How precise is the estimate of the effect? Is there a confidence interval?	1	1	1	1	1
11	Could there be confounding factors that have not been taken into account?	1	1	1	1	1
12	Can the results be applied to your research?	1	1	1	1	1
<b>Total</b>		<b>12</b>	<b>12</b>	<b>12</b>	<b>12</b>	<b>12</b>

Description:

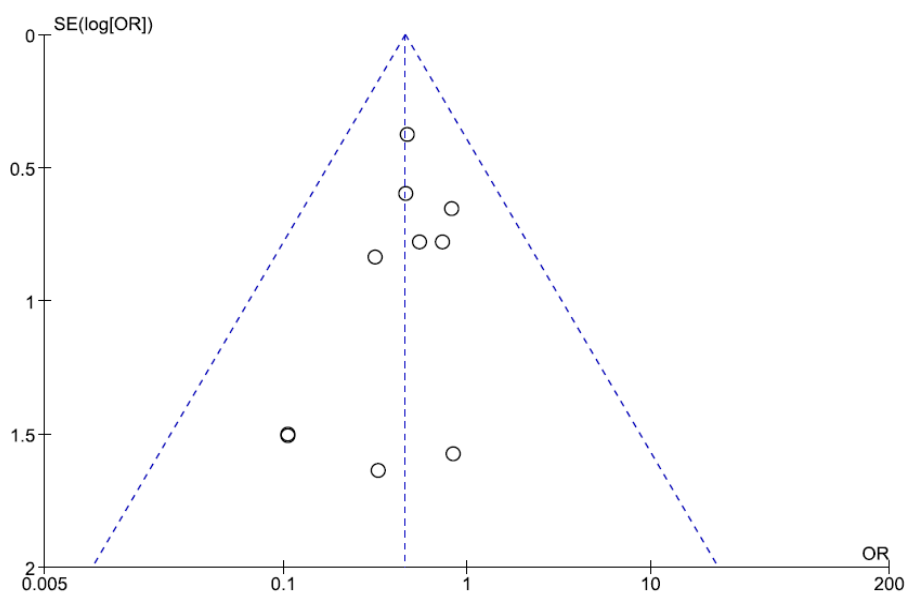
1: Yes

0: No

**Table 2. Summary Source of the Effectiveness of Ivermectin Use on Mortality in COVID-19 Patients**

No	Author	Country	Study Design	Total Sample		Population (P)	Intervention (I)	Comparison (C)	Outcome (O)
				COVID-19 Patients	Administration of Ivermectin				
1	Abd-Elsalam et al, 2021	Egypt	RCT	164	82	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
2	Elgazzar et al, 2020	Egypt	RCT	200	100	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
3	Gonzalez et al, 2021	Mexico	RCT	73	36	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
4	Gorial et al, 2020	Iraq	RCT	87	16	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
5	Hashim et al, 2020	Iraq	RCT	140	70	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
6	López-Medina et al, 2021	USA	RCT	398	200	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
7	Niaee et al, 2021	Iran	RCT	60	30	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
8	Okumuş et al, 2021	Turkey	RCT	66	36	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
9	Rajter et al, 2021	USA	RCT	296	98	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality
10	Ravikirti et al, 2021	India	RCT	112	55	COVID-19 confirmed patient	Ivermectin	Without Ivermectin	Mortality





**Figure 4. Funnel Plot of the Effectiveness of Ivermectin Use on Mortality in COVID-19 Patients**

**DISCUSSION**

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus (WHO, 2021). Coronavirus disease 2019 (COVID-19), caused by the new acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become the highest priority global pandemic. The number of cases in the world has more than 200 million people and about 5 million people have died (Johns Hopkins University of Medicine, 2021). Most people infected with the virus will develop mild to moderate respiratory illness and recover without requiring special treatment. However, some will become seriously ill and require medical attention. Patients with SARS-CoV-2 infection can show symptoms ranging from mild to severe with most of the population being asymptomatic carriers. The most commonly reported symptoms included fever (83%), cough (82%) and shortness of breath (31%) (Elgazzar, 2020). Transmission of SARS-CoV-2 occurs with high efficacy and infectivity, mainly through the respiratory route. Droplet transmission is the main known

route, although aerosols may represent another important route (Han et al., 2020). Confirmed cases of COVID-19 are performed by laboratory examinations Reverse-Transcriptase Polymerase-Chain-Reaction (RT-PCR) and Computed Tomography (CT) Scan of the chest (Hashim et al., 2020)

Ivermectin is an antiparasitic agent belonging to the avermectins group, originally a fermentable metabolite produced by the bacterium *Streptomyces avermitilis*. Ivermectin was introduced for medical use in 1982 and is elective against a wide variety of nematodes and helminths, and ectoparasites. Ivermectin is an FDA-approved broad-spectrum anti-parasitic agent that in recent years has been shown to have antiviral activity against a wide variety of viruses in vitro.

**The Effectiveness of Ivermectin Use on Mortality in COVID-19 Patients**

Based on the results of an analysis of 10 articles regarding the effectiveness of the use of ivermectin on mortality in COVID-19 patients, it was shown that administering ivermectin was effective in reducing the

average risk of death in COVID-19 patients. Based on the results of the analysis, there was no heterogeneity ( $I^2 = 0\%$ ;  $p = 0.940$ ) therefore, the Fixed Effect Model (FEM) is used. The use of ivermectin in COVID-19 patients reduced the median risk of death by 0.46 times compared to patients who were not given ivermectin (aOR= 0.46; 95% CI= 0.29 to 0.72;  $p < 0.001$ ).

An in vitro study conducted by Caly et al. (2020) showed that at 48 hours, this effect of ivermectin increased with the reduction of COVID-19 virus to a ~5000 times reduction in RNA virus in ivermectin-treated compared to control samples, indicating that ivermectin treatment resulted in the effective disappearance of all viral material at 48 hours. Consistent with this idea, no further reduction in RNA virus was observed at 72 hours. Overall, these results suggest that ivermectin has antiviral action against clinical isolates of SARS-CoV-2 in vitro, with a single dose being able to control viral replication within 24-48 hours in the system. Ultimately, the development of effective antivirals for SARS-CoV-2, if it is given to patients in early infection, it could help to limit viral loads, prevent progression of severe disease and limit person-to-person transmission.

This study is supported by Elgazzar et al. (2020) which stated that addition of Ivermectin to standard care is a highly effective drug for the treatment of COVID-19 patients with reductions in mortality, recovery time, and days of hospitalization compared to standard treatment only. Ivermectin has significantly reduced the incidence of infection in health care and household contacts by 2% compared with 10% in the non-ivermectin group when it is used as prophylactically.

Early use of Ivermectin is very useful for controlling COVID 19 infection. This is similar to a study reported by Gorial et al.,

(2020) which stated that additional use of Ivermectin (IVM) in standard care has a higher cure rate, shorter hospitalization days compared to controls. All patients in the IVM group recovered compared with controls [16 (100%) compared with no ivermectin 69 (97.2%)]. Two patients died in controls. In average, hospital stay was significantly lower in the IVM group compared to the control group (Mean= 7.62; SD= 2.75 compared with Mean= 13.22 SD= 5.90 days;  $p < 0.001$ ). No side effects were observed in this study.

This study is in line with Okumu et al. (2021) who found that patients with the addition of ivermectin to regular care (study group) had a higher rate of clinical improvement compared to patients who received only regular care (control group). At the end of the study, the mortality rate was found to be lower in the study group compared to the control group. However, the clinical improvement and mortality differences between the study and control groups were not statistically significant.

The study of Rajter et al (2021) supports this study with lower hospital mortality in the intervention group than in the placebo group. In 280 patients, 173 of them were treated with ivermectin and 107 were treated without ivermectin. Univariate analysis showed lower mortality in the ivermectin group (15.0% compared with no ivermectin 25.2%; OR= 0.52; 95% CI= 0.29 to 0.96;  $p = 0.030$ ). Mortality was also lower among ivermectin-treated patients with severe pulmonary involvement (38.8% versus 80.7% without ivermectin; OR= 0.15; 95% CI= 0.05 to 0.47;  $p = 0.001$ ). Ivermectin treatment is associated with lower mortality during COVID-19 treatment, especially in patients with severe pulmonary involvement.

Ravikirti et al. (2021) showed that a total of 115 patients were enrolled for the

study of which 112 were included in the final analysis. In addition, 55 of them were randomized to the intervention group while 57 were randomized to the placebo group. There was no significant difference in the baseline characteristics of the two arms. There was no significant difference in the primary results, which was the negative RT-PCR status on day 6 between the two groups. Similarly, there were no significant differences between the two groups in most of the secondary outcome measures, namely symptom status at day 6, discharge status at day 10, ICU admission, and need for invasive mechanical ventilation. However, while there were no in-hospital deaths in the intervention group, there were 4 deaths in the placebo group. As a result, all patients in the intervention group (n=56) were successfully discharged compared to the control group.

The meta-analysis conducted by Andrew et al. (2021) of 23 RCTs in 3,349 patients showed that ivermectin had a significant effect on faster viral clearance and a significant effect on limiting the duration of hospitalization. In the main analysis, excluding studies with a high risk of bias, there was no significant effect of ivermectin on survival or hospitalization (RR= 0.90; 95% CI= 0.57 to 1.42; p= 0.66) or hospitalization (RR= 0.63; 95%CI= 0.36 to 1.11; p= 0.110). Recently, preliminary results from a trial (Mills et al, 2021) showed in a randomized, placebo-controlled study of ivermectin in more than 1200 outpatients, there was no significant effect of ivermectin on hospitalization or survival.

A meta-analysis conducted by Kow et al. (2021) with 6 articles of randomized controlled trials, the results are in line with this study that ivermectin administration affects mortality reduction in COVID-19 patients (aOR= 0.21; 95% CI= 0.11 to 0.42). Several RCTs and observational studies

have reported faster virus clearance with ivermectin. However, other studies have not found this benefit. So, there is a need for further, larger studies to validate the results of this study

The limitation of the study is that there is a language bias, because the study only uses articles in English, thus ignoring studies in other languages. There is also database bias, because the databases used are PubMed, Science Direct, Google Scholar, and Springer Link, therefore, this study ignores other database sources.

#### **AUTHORS CONTRIBUTION**

Ayu Trisni Pamilih is the main researcher who choosed the topic, selected articles and study data. Didik Gunawan Tamtomo and Bhisma Murti analyzed the data and reviewed study documents.

#### **FUNDING AND SPONSORSHIP**

This study was self-funded.

#### **CONFLICT OF INTEREST**

There was no conflict of interest in this study.

#### **ACKNOWLEDGMENT**

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